

“Parenteral Fluid and Nutrition Therapy: Current Literature Review” is a comprehensive handbook covering references on four types of parenteral fluid therapy, namely resuscitation, repair, maintenance and parenteral nutrition. It is intended to provide an easy access for clinicians to understand the correct usage of various infusion solutions.

This handbook is a comprehensive quick reference of parenteral fluid and nutrition therapy for clinicians facing a diversity of hospitalized patients requiring individual intravenous fluid management, such as:

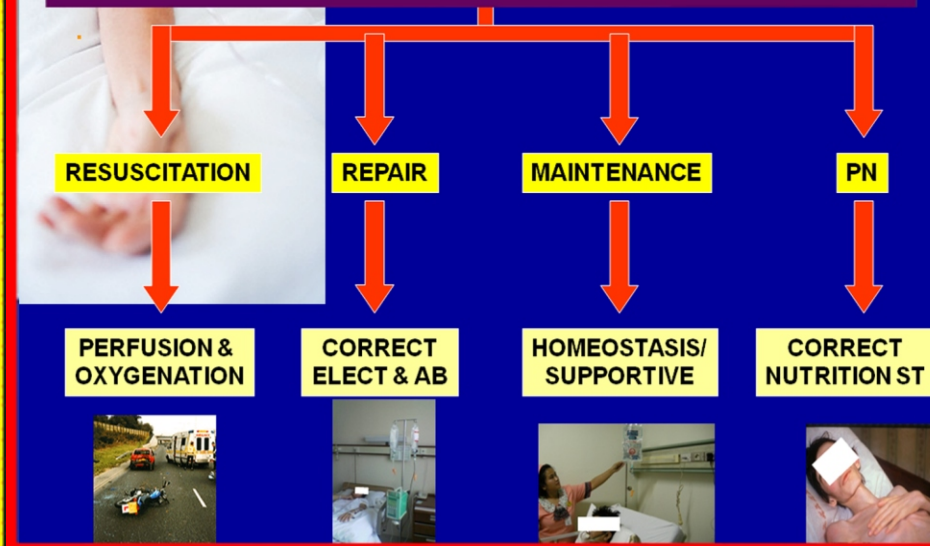
Management of Hemorrhagic Shock
 Hypotensive Fluid Resuscitation
 Colloid vs Crystalloid controversies
 Transfusion in critical illness
 Volume Replacement in various conditions
 Nutrition Support in various critical illnesses
 Sodium and potassium disorders
 Hypoglycemia and Hyperglycemia
 Update on Osmotherapy
 New Paradigm in Maintenance Fluid
 Perioperative Fluid Therapy
 Monitoring of Parenteral Fluid Therapy
 Phlebitis what causes and how to manage
 Extravasation Infiltration
 What is Protein Sparing effect?
 Insulin Resistance
 Miscellaneous

PARENTERAL FLUID AND NUTRITION THERAPY

1st Edition
2012

Current Literature Review

Parenteral Fluid & Nutrition Therapy



First Edition
2012

With the Compliments of

PT Otsuka Indonesia

Current Literature Review

PARENTERAL FLUID & NUTRITION THERAPY

**With the compliments of
PT Otsuka Indonesia**

Not for Commercial Purpose

Iyan Darmawan,MD

Medical Director PT Otsuka Indonesia

&

Budhi Santoso,MD

Senior Medical Advisor PT Otsuka Indonesia

First Edition

2012



PARENTERAL FLUID & NUTRITION THERAPY

(Current Literature Review)

© 2012 PT Otsuka Indonesia
All rights preserved

DISCLAIMER

The materials contained in this handbook are for educational and informational purposes only. They are not meant to imply or reflect guidelines for clinical care.

You agree that our company is not responsible for the success or failure of your decision making related to any information presented in this publication, or our products or services

FOREWORD

Clinicians in daily practice very commonly face seriously-ill patients with bleeding, fluid & electrolyte disorders and nutritional problem with high morbidity and mortality. Fluid and electrolyte problems include water and electrolyte loss due to diarrhea, intestinal obstruction, peritonitis, burn etc, while patients with trauma are very often accompanied with bleeding and hemorrhagic shock. Patients with dehydration due to diarrhea or intestinal obstruction have altered status of both fluid and electrolytes, and if not managed adequately patients may fall to shock and organ failure. Regarding the nutritional problem, almost 50% of patients come to surgical ward with malnutrition of various stages and 10-15% of them with severe malnutrition. It will increase the complications (morbidity & mortality), prolong hospital stay and increase the hospitalization cost by up to 75%.

To improve the outcome of the patients with bleeding, fluid-electrolyte and nutritional problem the clinician should master the knowledge and skill regarding the disease and problem related and its management. Current evidence-based findings should become the standard of reference in managing the patients. Lots of current textbooks and articles in the various journals provide the management of bleeding, fluid & electrolyte disorders and nutritional problem and can be accessed through the internet with or without payment. However, for busy clinicians, there will not be enough time to access the scientific information from internet, even not enough time to read the article or textbook rigorously. Therefore, a simple handbook regarding the bleeding, fluid-electrolyte and nutritional management in various common serious diseases is needed.

This book, as current literature review of Parenteral Fluid & Nutrition Therapy will be very helpful for busy clinicians as a quick reference or guidance to treat his/her patients with bleeding, fluid-electrolyte and

nutritional problem. This book also comes with the management of certain electrolyte problems which are very often faced by clinician, such as sodium and potassium disorders, and also problems related to parenteral nutrition, such as hyperglycemia and thrombophlebitis.

Clinicians are scientific persons and they should appraise critically every scientific information they read before using it for managing their patients. Therefore, should there be any doubtful or controversial information contained in this handbook, do not hesitate to write to the writers, to get clarification or further explanation.

Semarang, February 8th, 2012

Prof Dr.dr.Ignatius Riwanto Sp.B.KBD
Dept. of Surgery, Faculty of Medicine,
University of Diponegoro, Dr. Kariadi Hospital

PREFACE

One of the most challenging tasks of a clinician in the management of hospitalized patients is choosing the right parenteral fluid therapy, particularly in seriously ill patients. Correct administration and monitoring of resuscitation fluid therapy in emergency situation can be life saving. On the other hand, injudicious or incorrect use of intravenous fluids even in otherwise non-critical illnesses, may induce iatrogenic consequences and prolong hospitalization.

Nowadays, there have been so plenty types and brand names of infusion solutions in the market and often the rational selection for particular patients appears to be difficult.

Therefore, we take the liberty to provide reliable and accurate information to practicing doctors and other healthcare professionals in order to improve the quality of patient management. In addition, this handbook has been prepared and intended as well to fulfill the request of many practicing clinicians from various fields.

This handbook covers the four types of parenteral fluid therapy, namely resuscitation fluid therapy, repair fluid therapy, maintenance fluid therapy and parenteral nutrition therapy. Although we have tried to discuss many aspects of parenteral fluid therapy which have been compiled by medical advisors of the Leader in Infusion Therapy with many years of experience in the related scientific activities and medical writing, this handbook is still far from completeness and perfection and we look forward to receiving your feedback and criticism.

February, 2012
Editor

CONTENT/PAGE

RESUSCITATION FLUID THERAPY

1. Management of Hemorrhagic Shock 1
2. Hypotensive Fluid Resuscitation 15
3. Colloid vs Crystalloid controversies 19
4. Transfusion in critical illness 27
5. Volume Replacement in DHF 30
6. Fluid Resuscitation in DKA 35
7. Fluid Resuscitation in burn 38
8. Acetated Ringer in Burn: update reference 43
9. Severe malaria among children 46
10. Acetated Ringer's solution has beneficial effect in cardiac surgery 50
11. The effect of Asering in maintaining core body temperature in surgical patients 53

REPAIR FLUID THERAPY

1. Hyponatremia 56
2. Hyponatremia in Heart Failure 60
3. Hypernatremia 68
4. Hypokalemia 72
5. Bartter's Syndrome 82
6. SIADH 86
7. Diabetes Insipidus 93
8. Hypoglycemia in Children & Neonates 98
9. Update on Osmotherapy 106

MAINTENANCE FLUID THERAPY

1. New Paradigm in Maintenance Fluid Therapy 115
2. Why is provision of amino acids important during infection? 127
3. The Importance of Magnesium in hospitalized patients 133
4. Supportive fluid therapy in DHF 137
5. New Paradigm of postoperative maintenance fluid therapy 141
6. Parenteral Fluid Therapy in stroke patient 147
7. Stress Hyperglycemia in stroke patient 152
8. New Paradigm of Maintenance Fluid therapy in obstetric patient 159
9. Update on Clinical use of magnesium in obstetrics 171

10. Fluid balance in elderly patient 176
11. ESAS (Edmonton symptom assessment system) 180
12. Supportive Fluid therapy in most hospitalized patients 183
13. Fatigue, a hidden symptom of hospitalized patients 186
14. Cancer-related fatigue 192
15. Fluid and Elect therapy in cancer patients 198
16. Monitoring of Parenteral Fluid Therapy 202
17. Incompatibility of Infusion Solutions 210
18. Phlebitis: what causes and how to manage? 215
19. Extravasation & Infiltration 225

PARENTERAL NUTRITION THERAPY

1. What is Protein-Sparing effect? 231
2. BRANCHED-CHAIN AMINO ACIDS enhance the cognitive recovery of patients with severe traumatic brain injury 236
3. Insulin Resistance 241
4. Postoperative Insulin Resistance 249
5. Refeeding syndrome 255
6. Update on Nutrition Support in Trauma 258
7. Fluid and Nutrition Management in Acute Pancreatitis 265
8. Is Glutamine useful or harmful in head injury patients? 270
9. Glutamine Manages Side Effects of Cancer Treatment 277
10. Nutrition Support in the Elderly Hospitalized Patients 279
11. Update on Cancer Cachexia : Q & A 282
12. Sarcopenia 291
13. Nutritional support in septic patients 295
14. Nutritional support in Chronic Renal Failure 300
15. Nutritional Therapy in Burn Patient 304

INDEX 312-314

APPENDICES 315-318

ABOUT THE AUTHORS 319

MANAGEMENT OF HEMORRHAGIC SHOCK

Iyan Darmawan

Introduction

Shock is a state at which the cardiovascular system failure occurs that causes tissue perfusion disorder. This condition causes hypoxia, cellular metabolism disorders, tissue damage, organ failure and death.

Pathophysiology

Pathophysiology of hemorrhagic shock is a shortage of intravascular volume that causes a decrease in venous return resulting in decreased ventricular filling, decrease in stroke volume and cardiac output, resulting in tissue perfusion disorder.

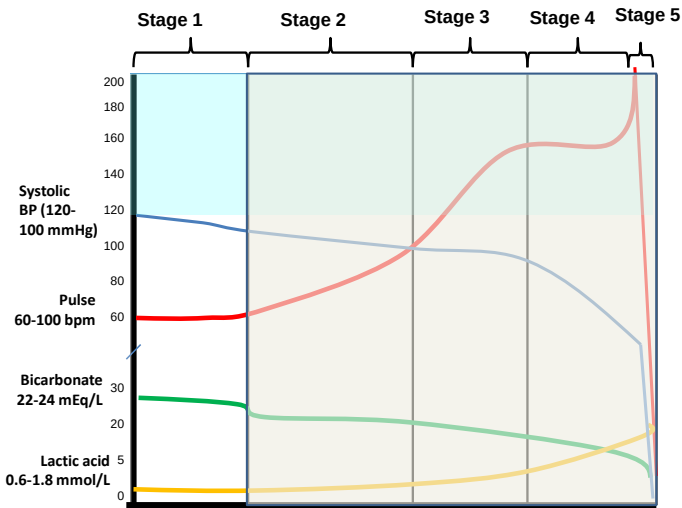
Resuscitation on hemorrhagic shock would reduce mortality. Management of hemorrhagic shock is intended to restore the circulating volume, tissue perfusion by correcting hemodynamics, control bleeding, stabilize the circulation volume, optimization of oxygen transport and if necessary giving vasoconstrictor when blood pressure remains low after the administration of fluid loading. Giving fluids are important in the management of hemorrhagic shock starting with crystalloid/ colloid followed by transfusion of blood components.

Coagulopathy associated with massive transfusion remains a significant clinical problem. Strategic therapy include maintaining tissue perfusion, correction of hypothermia and anemia, and the use of hemostatic products to correct microvascular bleeding.

STAGES OF SHOCK

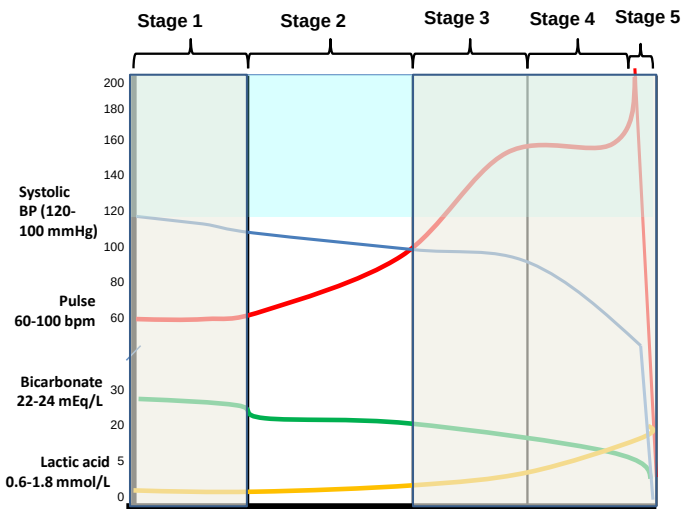
Shock has several stages before it becomes decompensated or irreversible condition, as described in the following figures:

STAGE 1 ANTICIPATION STAGE



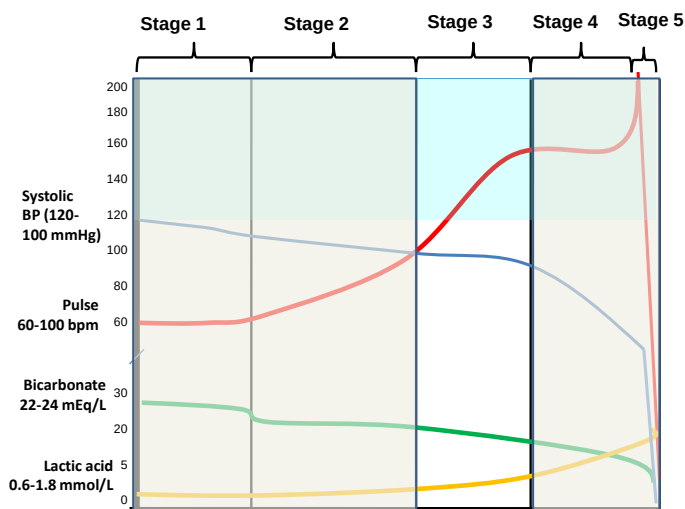
The disease has started but remains local Parameters are stable and within normal limits. There is usually enough time to diagnose and treat the underlying condition.

STAGE 2. PRE-SHOCK SLIDE



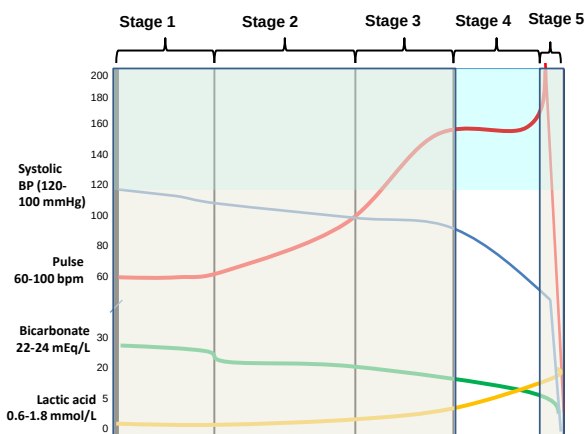
The disease is now systemic. Parameters drift, slip and slide... and start hugging the upper or lower limit of their normal range.

STAGE 3 COMPENSATED SHOCK



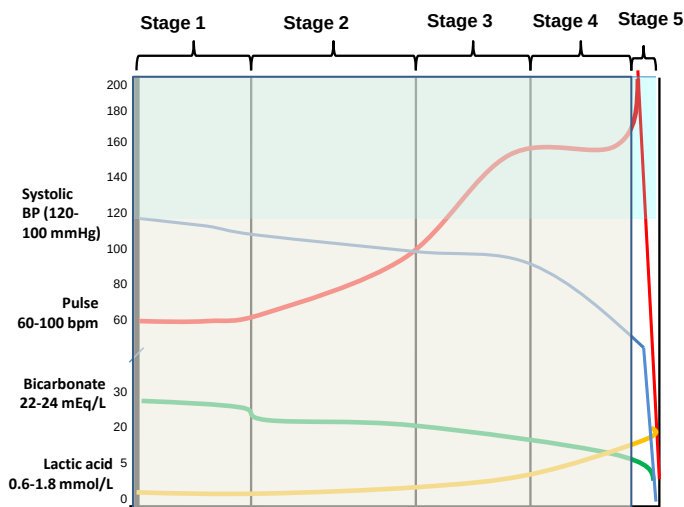
Compensated shock can start with low normal blood pressure: a condition called "normotensive, cryptic shock". Recognition of compensated shock is particularly important in patient with DHF. Clinicians should be alert on the following signs: Capillary refill time > 2 seconds; narrowing of pulse pressure, tachycardia, tachypnea and cold extremities.

STAGE 4 DECOMPENSATED SHOCK, REVERSIBLE



Now everybody call this "SHOCK" because hypotension is always present at this stage., Normotension can only be restored with intravenous fluid (if indicated) and/or vasopressors

STAGE 5 DECOMPENSATED IRREVERSIBLE SHOCK



Microvascular and organ damage are now irreversible (untreatable)

CLASSIFICATION OF SHOCK

The degree of hemorrhagic shock can be roughly estimated according to several clinical parameters, but a lot is determined by the response to fluid resuscitation ¹.

	Class 1	Class 2	Class 3	Class 4
Amount of Blood loss(ml)/%	Up to 750 Up to 15%	1000-1250 20-25%	1500-1800 30-35%	2000-2500 >40%
HR	72-84	>110	>120	>140
BP	118/72	110/80	70-90/50-60	Sys < 50-60
Resp rate	14-20	20-30	30-40	>35
Urine output/hr	30-35 ml	25-30 ml	5-15 ml	-
CNS	Slightly anxious	Anxious	Anxious & confused	Confused, lethargy
Lactic acid	Normal	Transition	Increased	increased

Management

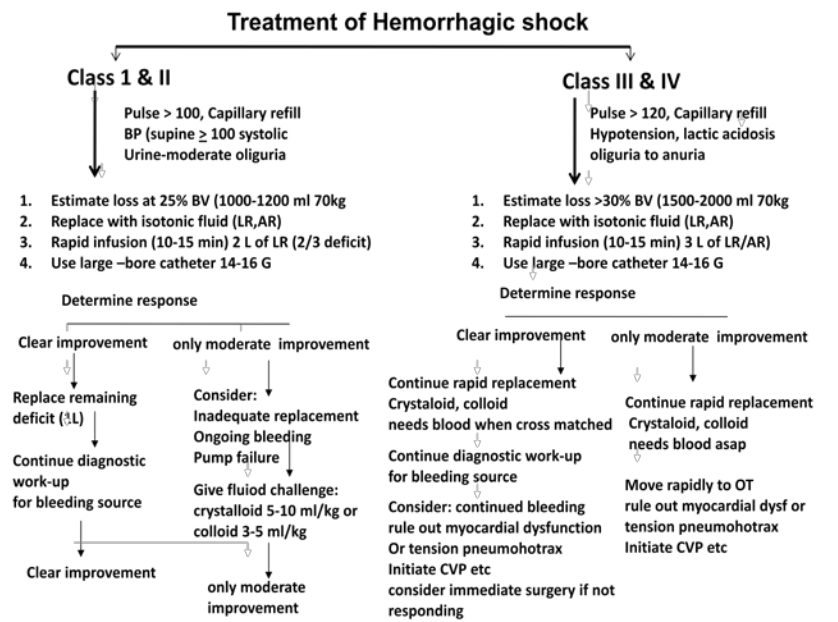
Initial therapy in the setting of acute hemorrhage should involve securing the airway, assuring adequate ventilation and oxygenation, controlling external bleeding (if present), and protecting the spinal cord (if potentially vulnerable). Fluid resuscitation should be determined with the following objectives in mind: (1) restoring intravascular volume sufficiently to reverse systemic hypoperfusion and limit regional hypoperfusion; (2) maintaining adequate oxygen-carrying capacity so that tissue oxygen delivery meets critical tissue oxygen demand; and (3) limiting ongoing loss of circulating RBCs. Unfortunately, there are no readily available precise parameters that allow the clinician to optimally balance these three objectives in the midst of the dynamic physiologic changes seen in acute hemorrhage and resuscitation. Nonetheless, the patient will most likely benefit from the clinician's best efforts to maintain this balance until surgical control of ongoing hemorrhage can be achieved.

Fluid Resuscitation

Intravascular volume replacement to treat hemorrhage has been the accepted dogma for decades. The goal of restoring normal intravascular volume and normal arterial blood pressure was generally accepted for most of this time. The major area of controversy was the optimal resuscitation fluid. However, over the past decade the accepted practice of resuscitating patients to a normal blood pressure has been questioned. The early studies that supported aggressive volume replacement were performed in laboratory models of controlled hemorrhage. In such a circumstance, rapidly restoring normovolemia optimized outcome and had no appreciable adverse effects.² However, this laboratory model does not accurately reflect the clinical situation. Most hemorrhagic shock patients have not had control of their bleeding achieved prior to initiation of fluid

resuscitation. This fact raised concern that fluid resuscitation to a normal blood pressure might actually be deleterious by exacerbating ongoing hemorrhage and ultimately worsening outcome. Formation of clots at areas of vascular injury is facilitated by the lower blood pressure that results during hemorrhage. Increased blood pressure may dislodge these fragile developing clots. Because crystalloid solutions have essentially no oxygen-carrying capacity, any exacerbation of hemorrhage resulting from their infusion will lower the oxygen-carrying capacity of the circulating blood. Laboratory models of acute vascular injury with uncontrolled hemorrhage verified that raising the arterial blood pressure to the normal range increased the rate of ongoing bleeding. This led to the concept of limited volume or "hypotensive" resuscitation..³

The goal of this limited approach is to provide sufficient fluid resuscitation to maintain vital organ perfusion and



avoid cardiovascular collapse while keeping the arterial blood pressure relatively low (e.g., mean arterial pressure of 60 mm Hg) in the hope of limiting further loss of red blood cells until surgical control of bleeding can be achieved. The potential adverse effect of this approach is that it accepts the presence of regional hypoperfusion, the effects of which are dependent on both the severity and duration of the hypoperfusion. Splanchnic hypoperfusion is especially of concern because this may be a major contributor to the development of subsequent multiple organ dysfunction.¹ Unfortunately, accurate clinical assessment of regional hypoperfusion is not presently possible. Thus, the optimal resuscitation end point is not clear and likely varies with the individual patient. A randomized clinical study that aimed to evaluate hypotensive resuscitation to a systolic blood pressure of 70 mm Hg did not show any mortality benefit for this approach. However, the target pressure of 70 mm Hg was difficult to maintain, with the systolic blood pressure in the hypotensive group reaching an average of 100 mm Hg. This demonstrates the difficulty of achieving and maintaining a specific hypotensive blood pressure target in the dynamic setting of hemorrhagic shock resuscitation. At present, this is still a concept that has not been clearly shown to improve survival. However, it seems reasonable to keep this concept in mind and to avoid excessive fluid resuscitation.

Blood Transfusion

There are no clearly defined parameters that trigger the switch from crystalloid to blood resuscitation. However, it is generally accepted that a patient in shock that demonstrates minimal or only modest hemodynamic improvement after rapid infusion of 2 to 3 L of crystalloid is in need of blood transfusion. However, it would be acceptable to start blood immediately if it is clear that the patient has suffered profound blood loss and is on the verge of cardiovascular collapse. Some patients may have an adequate hemodynamic response to initial

crystalloid therapy that is transient. In such cases, continued crystalloid infusion beyond the first 2 to 3 L might be used for hemodynamic support so long as attention is paid to progressive hemodilution and its effect on tissue oxygen delivery. This hemodilution also lowers the concentration of clotting factors and platelets needed for intrinsic hemostasis at bleeding sites. Serial assessment of blood hemoglobin concentration is useful in such a situation. An American Society of Anesthesiologists task force review found that a blood hemoglobin concentration >10 g/dL (hematocrit >30 percent) very seldom requires blood transfusion, whereas a level <6 g/dL (hematocrit <18 percent) almost always requires blood transfusion. This leaves a rather wide intermediate range of hemoglobin—between 6 and 10 g/dL—where the decision to administer blood is significantly influenced by other factors, such as the presence of underlying disease processes that are sensitive to decreased tissue oxygen delivery and the rate of continued blood loss, if present. Understandably, as the hemoglobin concentration decreases, especially to 8 g/dL or less, the likelihood of needing blood markedly increases.

When possible, typed and cross-matched blood is preferable. However, in the acute setting where time does not permit full cross-matching, type-specific blood is the next best option followed by low-titer O-negative blood. Blood can be administered as whole blood or packed RBC preparations. In U.S. blood banks, whole blood is not stocked, and only packed RBCs are available. In the setting of massive hemorrhage with large volumes of crystalloid and blood resuscitation, fresh-frozen plasma and platelet transfusions may be needed to reverse the associated dilutional coagulopathy.

Red blood cell transfusion obviously restores lost hemoglobin, but stored blood components may also not be fully functional and can have adverse effects, which

appear to be exacerbated with longer storage time.⁸ Using current preservatives, RBCs can be stored for up to 42 days and it has been reported that the average age of a unit of blood administered in the United States is approximately 21 days old. Stored RBCs can lose deformability, which can limit their ability to pass normally through capillary beds, or can cause capillary plugging. The oxygen dissociation curve is altered by loss of 2,3-diphosphoglycerate in the erythrocyte, which adversely affects the off-loading of oxygen at the tissue level. Clinical studies report worsening of splanchnic ischemia and an increased incidence of multiple-organ dysfunction associated with transfusion of RBCs that have been stored for longer than 2 weeks. Therefore, RBC transfusion, although a critical intervention in severe hemorrhagic shock, has limitations and potential adverse effects.

Transfusion of packed red blood cells and other blood products is essential in the treatment of patients in hemorrhagic shock. Current recommendations in stable ICU patients aim for a target hemoglobin of 7 to 9 g/dL;⁵ however, no prospective randomized trials have compared restrictive and liberal transfusion regimens in trauma patients with hemorrhagic shock. Fresh frozen plasma (FFP) should also be transfused in patients with massive bleeding or bleeding with increases in prothrombin or activated partial thromboplastin times 1.5 times greater than control. Civilian trauma data show that severity of coagulopathy early after ICU admission is predictive of mortality. Evolving data suggest more liberal transfusion of FFP in bleeding patients, but the clinical efficacy of FFP requires further investigation. Recent data collected from a U.S. Army combat support hospital in patients that received massive transfusion of packed red blood cells (>10 units in 24 hours) suggests that a high plasma to RBC ratio (1:1.4 units) was independently associated with improved survival. Platelets should be transfused in the bleeding patient to maintain counts above $50 \times 10^9/L$. There is a potential

role for other blood products, such as fibrinogen concentrate or cryoprecipitate, if bleeding is accompanied by a drop in fibrinogen levels to less than 1 g/L. Pharmacologic agents such as recombinant activated coagulation factor 7, and antifibrinolytic agents such as -aminocaproic acid, tranexamic acid (both are synthetic lysine analogues that are competitive inhibitors of plasmin and plasminogen), and aprotinin (protease inhibitor) may all have potential benefits in severe hemorrhage but require further investigation.

Colloid Resuscitation

Several colloid agents have been studied experimentally and used clinically for the treatment of hemorrhagic shock. Colloids have larger molecular weight particles with plasma oncotic pressures similar to normal plasma proteins. Therefore, colloids would be expected to remain in the intravascular space, replacing plasma proteins lost as a consequence of hemorrhage, and more effectively restore circulating blood volume than crystalloid solutions. An argument favoring the use of colloids has been the concern that extravascular shift of infused crystalloid solutions has potential adverse effects, including pulmonary interstitial edema with impaired oxygen diffusion and intraabdominal edema with diminished bowel perfusion. However, pathologic conditions, such as hemorrhagic shock and sepsis, lead to increased vascular permeability that can allow for extravascular leakage of these larger colloid molecules.

Colloid vs Crystalloid controversies : Some additional information

The choice of colloids vs crystalloids for volume resuscitation has long been a subject of debate among critical care practitioners, primarily because there are data to support arguments for both forms of therapy. In 1998, the British Medical Journal published a meta-analysis on the use of albumin in the critically ill patient;

30 randomized, controlled trials (RCTs) involving 1419 patients were analyzed. The conclusion was that albumin may actually increase mortality, noted Timothy Evans, MD. This review had an impact on practice, influencing clinicians to use less albumin, but was later criticized as being flawed when subsequent reviews did not substantiate the authors' conclusion⁶. Recently, the completion of the Saline vs Albumin Fluid Evaluation (SAFE) study has shed new light on this issue.

With the availability of various colloids with different physicochemical properties, controversy of colloid versus crystalloid has become an additional issue.⁷

Summarized below are advantages and disadvantages of both colloids and crystalloids.

Colloids

Advantages	Disadvantages
1. Plasma volume expansion without concomitant ISF expansion	1. Anaphylaxis
2. Greater intravascular volume expansion for a given volume	2. Expensive
3. Longer duration of action	3. Albumin can aggravate myocardial depression in shock patient, owing to albumin binding to Ca^{++} , which in turn decreases ionic calcium
4. Better tissue oxygenation	4. Possible coagulopathy, impaired cross matching
5. Less alveolar-arterial O_2 gradient	

Crystalloids

Advantages	Disadvantages
1. Easily available	1. Weaker and shorter volume effect compared to colloid
2. Composition resembling plasma (acetated ringer, lactated)	2. decreased tissue oxygenation, owing to increased distance between microcirculation and tissue

ringer)	
3. Easy storage at room temperature	
4. Free of anaphylactic reaction	
5. Economical	

Although interstitial edema is a more potential complication after crystalloid resuscitation, UP TO NOW, there are no physiological, clinical and radiological evidence that colloid is better than crystalloid in term of pulmonary edema..

The SAFE Study

In a recent meta-analysis, an overall excess mortality of 6% was observed in patients who were treated with albumin. These findings generated considerable discussion and controversy, which led to the design and implementation of the SAFE study, presented by Simon Finfer, MD.⁷ This double-blind RCT enrolled 7000 patients from 16 ICUs in Australia and New Zealand over an 18-month period. Patients were randomized to receive either 4% human albumin or normal saline from time of admission to the ICU until death or discharge. In the first 4 days, the ratio of albumin to saline was 1:1.4, meaning that the volumes (colloids vs crystalloids) were not significantly different, contrary to what was expected. Notably, there was no difference between the 2 groups in 28-day all-cause mortality. Mean arterial blood pressure, central venous pressure, heart rate, and incidence of new organ failure were also similar in both groups.

In a subgroup analysis, differences between trauma and sepsis patients were observed. The relative risk (RR) of death in patients with severe sepsis who received albumin vs saline was 0.87. The RR of death in albumin-treated patients without severe sepsis was 1.05 (P = .059). The results were the opposite in trauma patients.

The overall mortality rate in trauma patients was higher when albumin vs saline was used for volume resuscitation (13.5% vs 10%, $P = .055$). When patients with traumatic brain injury (TBI) were studied separately, the mortality rate was 24.6% in patients who were treated with albumin compared with 15% in patients who were treated with saline (RR 1.62, 95% confidence interval, -1.12 to 2.34, $P = .009$). Furthermore, when TBI patients were excluded, there were no differences in mortality rates among trauma patients.

Based on these results, the administration of albumin appears to be safe for up to 28 days in a heterogeneous population of critically ill patients, and may be beneficial in patients with severe sepsis. However, the safety of albumin administration has not been established in patients with traumatic injury, including TBI. Although the differences in mortality rates in trauma and TBI patients were observed in a subgroup analysis and consequently have limited validity, this is a strong signal, especially in TBI patients. A new study, SAFE Brains, has been designed to examine these differences

What are the goals of resuscitation fluid therapy (resuscitation endpoints)?

The success criteria of management of hemorrhagic shock, or particularly fluid resuscitation therapy can be assessed from the following parameters:

- Capillary refill time < 2 seconds
- MAP 65-70 mmHg
- O_2 sat >95%
- Urine output >0.5 ml/kg/hour (adults) ; > 1 ml/kg/hour (children)
- Shock index = HR/SBP (normal 0.5-0.7)
- CVP 8 to 12 mm Hg
- $ScvO_2$ > 70%

CONCLUSION

Resuscitation fluid therapy in patients with hemorrhagic shock should receive more serious attention to reduce mortality and morbidity. The things to put into consideration are:

1. Understand the stages of hypovolemic shock and associated pathophysiological changes
2. Early detection of compensated shock so that fluid can be given adequately
3. Know how much fluid crystalloid / colloid must be given
4. Indication of blood transfusion
5. How to know the success of resuscitation.

References:

1. Demling RH, Wilson RF.: Decision Making in Surgical Critical Care. B.C. Decker Inc, 1988. p 64.
2. Tintinalli JE. Tintinalli's Emergency Medicine: A comprehensive Study Guide, 6th edition
3. Stern SA: Low-volume fluid resuscitation for presumed hemorrhagic shock: Helpful or harmful? Curr Opin Crit Care 7:422, 2001.
4. Dutton RP, Mackenzie CF, Scalea TM: Hypotensive resuscitation during active hemorrhage: Impact on in-hospital mortality. J Trauma 52:1141, 2002.
5. Brunicki, FC. Et al. Schwartz's Principles of Surgery, 9e
6. Liolios A. Volume Resuscitation: The Crystalloid vs Colloid Debate Revisited. Medscape 2004
7. SAFE Study Investigators: A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004, 350:2247-2256

HYPOTENSIVE FLUID RESUSCITATION

Iyan Darmawan

Introduction

Fluid resuscitation with either isotonic crystalloids (such as Acetated Ringer's, Lactated Ringer's and Normal Saline) or colloids is still the mainstay of management of hemorrhagic shock. Recently, the rate and types of fluid for trauma patients has become controversial. Aggressive IV fluid resuscitation to combat shock has been the Advanced Trauma Life Support (ATLS)¹ standard of practice for many years. However, 2006 Joint Royal Colleges Ambulance Liaison Committee (JRCALC)² Guidelines suggest that pre-hospital IV fluid be only sufficient to keep a systolic blood pressure 80-90 mmHg. Avoidance of hypotension is an important principle in the initial management of blunt trauma patients particularly with TBI. On the other hand, in penetrating trauma with hemorrhage, delaying aggressive fluid resuscitation until definitive control may prevent additional bleeding.³

Hypotensive Resuscitation versus Aggressive Resuscitation

Previously, the initial management of hypovolaemia in the trauma patient involved the rapid administration of 2000 ml of Ringer's lactate as an initial fluid challenge.¹ More recently, there have been changes in practice such that the initial fluid resuscitation of the patient is gauged by palpation of the radial pulse. Fluid boluses of up to 250 ml are given to maintain the radial pulse, as required. In general, the radial pulse is palpable when the systolic blood pressure is >70 mmHg, which is sufficient to maintain cerebral and myocardial perfusion in the short term. This is referred to as hypotensive resuscitation, or permissive hypotension, and is one of the components of damage control resuscitation. The use of small volumes of fluid avoids hemodilution and

reduces the risk of coagulopathy. A lower systolic blood pressure will allow primary blood clots to form more easily and reduces the risk of secondary hemorrhage if the blood pressure rises before surgical control of the source of hemorrhage is obtained.⁴

Definition of Hypotensive Resuscitation

In hypotensive resuscitation strategy the target mean arterial pressure (MAP) was 50 mm Hg. Those in the control (high MAP [HMAP]) arm were managed with standard fluid resuscitation to a target MAP of 65 mm Hg.⁵

Rationale for Hypotensive resuscitation:

- Excessive fluid resuscitation increases the chances of developing abdominal compartment syndrome in critically ill surgical/trauma, burn, and medical patients.
- An important danger in penetrating large vessel injury is that the improvement in hemodynamics brought about by administration of fluid will cause primary extraluminal thrombus to be dislodged.^{6,7}
- Similarly, in a multicenter study of burn patients, administration of excessive fluids (in excess of 25% of predicted) increased the odds of ARDS (odds ratio [OR] 1.7), pneumonia (OR 5.7), multiple organ failure (OR 1.6), bloodstream infections (OR 2.9), and death (OR 5.3).⁸
- Hypotensive resuscitation strategy reduces transfusion requirements and severe postoperative coagulopathy in trauma patients with hemorrhagic shock: preliminary results of a randomized controlled trial.⁵
- A systematic review of 52 animal trials concluded that fluid resuscitation appeared to decrease the risk of death in models of severe hemorrhage (RR= 0.48), but increased the risk of death in those with less severe hemorrhage (RR = 1.86).⁹

The concept of hypotensive resuscitation or delayed resuscitation applies well to young patients, especially following penetrating trauma. However, blunt trauma

patients often have traumatic brain injury (TBI) that may be exacerbated by hypotension. Similarly, elderly patients with coronary or carotid arterial disease may not be able to safely tolerate hypotension. However, even in these patients excessive volume loading can stress the cardiopulmonary reserve (eg, congestive heart failure, pulmonary edema), worsen pulmonary contusions, and increase the chances of developing other complications, such as compartment syndrome.

Small volume Resuscitation with Hypertonic Saline

The earliest use of hypertonic saline solution (HSS) for patient resuscitation was described some 25 years ago. Interestingly, current use of HSS was initiated by a nursing error when a Brazilian nurse inadvertently gave an unconscious shocked dialysis patient 100mls of 7.5% saline, whereupon a minute later the patient regained consciousness and a normal blood pressure. Subsequently experimental and clinical research work has led to acceptance of the use of HSS for resuscitation in clinical practice. Sakwari et al ¹⁰ reported the results of forty five patients who were enrolled and resuscitated with 250 mls 7.5% HSS. Among the studied patients, 88.9% recovered from shock immediately after being infused with 7.5% HSS. Of patients with a single injury, 96.6% recovered from shock whereas only 75% of those with multiple injuries recovered. Eighty percent of patients survived beyond 24 hours post resuscitation. While 93.1% of patients with a single injury survived beyond 24 hours, only 56.3% of those who sustained multiple injuries did so.

It was concluded that rapid resuscitation with HSS has demonstrated clinical benefits in initial treatment of traumatic hemorrhagic shock in patients admitted to the emergency room. Further investigation of the effects of HSS resuscitation is warranted.

Conclusion:

Hypotensive fluid resuscitation is increasingly used nowadays with better outcome in young patients especially following penetrating trauma, but cannot be implemented universally for every patient with trauma. Clinical judgment and anticipation of length of time required before reaching definitive surgical treatment is crucial before initiating fluid resuscitation.

References:

1. Advanced Trauma Life Support for Doctors. Student Course Manual. American College of Surgeons Committee on Trauma. 2008 8th edition.
2. Fisher JD, Brown SN, Cooke MW. UK Ambulatory Service Clinical Practice Guidelines, JRCACL 2006.
3. Bickell WH, et al Immediate versus Delayed Fluid Resuscitation for Hypotensive Patients with Penetrating Torso Injuries.NJEM. Volume 331:1105-1109 October 27, 1994 Number 17
4. Duncan NS, Moran C. Initial resuscitation of the trauma victim. MINI-SYMPOSIUM: BASIC SCIENCE OF TRAUMA ORTHOPAEDICS AND TRAUMA 24:1 ELSEVIER 2009
5. Morrison CA, Carrick MM, Norman MA, Scott BG, Welsh FJ, Tsai P, Liscum KR, Wall MJ, Mattox KL J Trauma 2011 Mar; 70(3):652-63.
6. Bickell WH, Bruttig SP, Millnamow GA, et al. The detrimental effects of intravenous crystalloid after aortotomy in swine. Surgery 1991;110:529-36
7. Revell M, et al. Fluid resuscitation in prehospital trauma care: a consensus view. Emerg Med J 2002; 19:494-498
8. Alam HB, Velmahos GC. New Trends in Resuscitation. Curr Probl Surg 2011;48(8):531-564
9. Alam HB Advances in resuscitation strategies International Journal of Surgery 9 (2011) 5 -12
10. Sakwari¹,V.;Mkony²,C.&Mwafongo³,V Rapid Resuscitation with Small Volume Hypertonic Saline Solution for Patients in Traumatic Haemorrhagic Shock. *East and Central African Journal of Surgery*, Vol. 12, No. 1, April, 2006, pp. 131-138

COLLOID VS CRYSTALLOID CONTROVERSIES:

SOME ADDITIONAL INFORMATION

Iyan Darmawan

Introduction

The choice of colloids vs crystalloids for volume resuscitation has long been a subject of debate among critical care practitioners, primarily because there are data to support arguments for both forms of therapy. In 1998, the British Medical Journal published a meta-analysis on the use of albumin in the critically ill patient; 30 randomized, controlled trials (RCTs) involving 1419 patients were analyzed. The conclusion was that albumin may actually increase mortality. This review had an impact on practice, influencing clinicians to use less albumin, but was later criticized as being flawed when subsequent reviews did not substantiate the authors' conclusion. The Saline vs Albumin Fluid Evaluation (SAFE) study has clarified this issue.

There is no evidence yet from RCTs that resuscitation with colloids reduces the risk of death, compared to resuscitation with crystalloids, in patients with trauma, burns or following surgery. As colloids are not associated with an improvement in survival, and as they are more expensive than crystalloids, it is hard to see how their continued use in these patients can be justified outside the context of RCTs ¹

Past Controversies

Summarized below are advantages and disadvantages of both colloids and crystalloids

Colloids

Advantages	Disadvantages
1. Plasma volume expansion without concomitant ISF	1. Anaphylaxis 2. Expensive

expansion	3. Albumin can aggravate myocardial depression in shock patients, owing to albumin binding to Ca^{++} , which in turn decreases ionic calcium
2. Greater intravascular volume expansion for a given volume	4. Possible coagulopathy, impaired cross matching
3. Longer duration of action	
4. Better tissue oxygenation	
5. Less alveolar-arterial O_2 gradient	

Crystalloids

Advantages	Disadvantages
1. easily available	1. weaker and shorter volume effect compared to colloid
2. composition resembling plasma (acetated ringer, lactated ringer)	2. decreased tissue oxygenation, owing to increased distance between microcirculation and tissue
3. easy storage at room temperature	
4. free of anaphylactic reaction	
5. economical	

Although interstitial edema is a more potential complication after crystalloid resuscitation, UP TO NOW, there are no physiological, clinical and radiological evidence that colloid is better than crystalloid in term of pulmonary edema.

Theoretical advantages of Albumin have been cited, including:

- Anti-inflammatory and Antioxidant Properties
- Diminish Lung permeability in patients with ALI and adult respiratory distress syndrome (ARDS).

Albumin functions as a hyperoncotic volume expander and, when combined with furosemide, can augment fluid shifts. In an unpublished study of 24 septic patients, a 200-mL bolus of 20% albumin significantly increased the cardiac index within 1 minute. This increase was not sustained, however, but progressively declined over the next 30 minutes, noted Dr. Soni. The same effects were observed with changes in the pulmonary artery pressure and the pO_2 . In another study of 37 patients with ALI, furosemide and albumin were administered concomitantly, resulting in significant weight loss and improved pO_2/FIO_2 ratio. However, no differences in mortality were observed.

Volume Expansion in the Patient With ALI

ALI is a common complication after blood loss or sepsis, noted Arthur Slutsky, MD. ALI is associated with increased inflammatory cytokine production and the release of oxygen free radicals. Both severe sepsis and severe blood loss can lead to hypotension and the subsequent need for endotracheal intubation, but it is not clear what fluid is optimal for volume resuscitation in patients with ALI. Crystalloids leak into the extravascular space; however, in addition to avoiding third-spacing of fluids, albumin possesses anti-inflammatory and free radical scavenger properties.

The beneficial effect of albumin seen in the hemorrhagic shock model was almost absent in the endotoxic shock model. It appears that resuscitation with albumin may have a role in ameliorating ventilator-induced ALI after hemorrhagic shock, but not after endotoxic shock.

In a 2-center, prospective, double-blind, placebo-controlled RCT by Martin and colleagues, the effects of albumin and furosemide were evaluated in 37 hypoproteinemic, mechanically ventilated patients with ALI and serum total protein ≤ 5.0 g/dL. Patients were given either 25 g of albumin every 8 hours with continuous furosemide diuresis or placebo. There was no difference in mortality between the groups, but there were significant differences in fluid balance, oxygenation, and hemodynamic parameters, favoring the albumin plus furosemide-treated group. Collectively, these data suggest that albumin might have a beneficial effect on ventilator-induced lung injury in the hemorrhagic shock model or on lung function in hypoproteinemic patients with ALI. Larger RCTs are warranted.²

In the ICU, patients with septic shock were resuscitated with a combination of crystalloids, colloids and blood products. Although the more severely shocked patients received higher volumes of crystalloids, colloids and blood products, mortality did not differ between the groups.³

The SAFE Study

In a meta-analysis, an overall excess mortality of 6% was observed in patients who were treated with albumin. These

findings generated considerable discussion and controversy, which led to the design and implementation of the SAFE study. This double-blind RCT enrolled 7000 patients over an 18-month period. Patients were randomized to receive either 4% human albumin or normal saline from time of admission to the ICU until death or discharge. In the first 4 days, the ratio of albumin to saline was 1:1.4, meaning that the volumes (colloids vs crystalloids) were not significantly different, contrary to what was expected. Notably, there was no difference between the 2 groups in 28-day all-cause mortality. Mean arterial blood pressure, central venous pressure, heart rate, and incidence of new organ failure were also similar in both groups.

In a subgroup analysis, differences between trauma and sepsis patients were observed. The relative risk (RR) of death in patients with severe sepsis who received albumin vs saline was 0.87. The RR of death in albumin-treated patients without severe sepsis was 1.05 ($P = .059$). The results were the opposite in trauma patients. The overall mortality rate in trauma patients was higher when albumin vs saline was used for volume resuscitation (13.5% vs 10%, $P = .055$). When patients with traumatic brain injury (TBI) were studied separately, the mortality rate was 24.6% in patients who were treated with albumin compared with 15% in patients who were treated with saline (RR 1.62, 95% confidence interval, -1.12 to 2.34, $P = .009$). Furthermore, when TBI patients were excluded, there were no differences in mortality rates among trauma patients.

Based on these results, the administration of albumin appears to be safe for up to 28 days in a heterogeneous population of critically ill patients, and may be beneficial in patients with severe sepsis. However, the safety of albumin administration has not been established in patients with traumatic injury, including TBI. Although the differences in mortality rates in trauma and TBI patients were observed in a subgroup analysis and consequently have limited validity, this is a strong signal, especially in TBI patients. A new study, SAFE Brains, has been designed to examine these differences.

Volume Expansion in the Hypoalbuminemic Patient

The Sepsis Occurrence in Acutely Ill Patients (SOAP) study, an observational study, documented significant variability in the amount of albumin administered in ICUs in Europe. Furthermore, patients who received albumin had a higher mortality rate, which may be explained by the fact that they were sicker to begin with. Possible reasons for greater severity of illness included fluid overload, altered myocardial contractility, worsening of edema, impaired water and sodium excretion, and altered immune response.

Critically ill patients commonly have hypoalbuminemia secondary to inflammation, liver dysfunction, malnutrition, capillary leakage, and the production of acute-phase reactants. Hypoalbuminemia is an important clinical problem because it is associated with anergy, diarrhea, prolonged ICU stay, and increased mortality. In a meta-analysis of 90 cohort studies involving 291,433 patients, it was concluded that hypoalbuminemia is associated with poor clinical outcomes and that albumin should be used whenever clinically indicated. In the same meta-analysis, 9 prospective controlled trials with 535 total patients were also reviewed. In these studies, hypoalbuminemia was corrected and there was the suggestion that complication rates may be reduced when the serum albumin level attained during albumin administration exceeds 30 g/L.⁴

Effects of various colloidal and hypertonic solutions on microcirculation

Changes in vascular permeability can influence plasma volume and affect the degree of oedema in the body. In diseases with an increased vascular permeability, adequate fluid therapy is of considerable importance to prevent hypovolaemia. Mechanisms behind differences in effectiveness of various plasma volume expanders to restore a low plasma volume microcirculation are still not fully understood. Hollbeck of Lund University Hospital conducted an experiment in 2001 by analysing colloid and hypertonic plasma volume expanders regarding their effects on transvascular fluid exchange and vascular permeability in skeletal muscle during and after discontinuation of the infusions. In addition, permeability effects are analysed in skeletal muscle following endotoxin infusion, as well as effects of plasma volume substitution on intestinal perfusion and

metabolism in endotoxaemia. Capillary filtration coefficient measurements showed that fluid permeability is decreased by albumin and dextran, unchanged by hydroxyethyl starch (HES), and increased by gelatin. Measurements of change in the reflection coefficient for albumin showed no direct effect on albumin permeability of dextran, gelatin, or hydroxyethyl starch. Hypertonic saline increased fluid permeability an effect not seen with mannitol and urea. Muscle volume was decreased by 20% albumin, unchanged by 6% dextran 70 and 6% HES 200/0.5, and increased by 3.5% gelatin. Gelatin and HES, but not dextran and albumin induced rebound filtration, indicating interstitial accumulation of the colloid molecules. Hypertonic saline, mannitol and urea induced absorption of which hypertonic saline was most effective and mannitol less effective over time in relation to osmotic capacity. Mannitol and urea but not hypertonic saline showed rebound filtration indicating intracellular accumulation of mannitol and urea. During endotoxaemia, both fluid and albumin permeability increased in skeletal muscle and hypovolaemia was shown to be the major, but probably not the only cause of disturbed intestinal perfusion. No difference could be seen between albumin, dextran, and hydroxyethyl starch in effectiveness to restore intestinal perfusion during endotoxaemia.⁵

Transvascular Exchange and Organ Perfusion

	6% Dextran 70	HE S	Gel- atin	Alb- umin	Man- nitol	Urea	HS
Fluid permeability	↓	u	↑	↓	u	u	↑
Albumin permeability	u	u	u				
Muscle volume	u	u	↑ 35%	↓ 20%			
Rebound filtration	-	+	+	-	+	+	-

U = unchanged; HS =hypertonic saline; HES=hydroxyethyl starch

Effects of various colloids on renal function

All colloidal solutions, including hyperoncotic human albumin (20% or 25% HA) can induce acute renal failure (ARF) by increasing the plasma colloid osmotic pressure. This condition has been coined "hyperoncotic ARF". Dehydrated patients receiving large amount of hyperoncotic colloid without addition of crystalloid are prone to develop hyperoncotic ARF. Only one study investigated nonsurgical, non-ICU patients. The renal effects of 20% HA, dextran 70, and polygeline were evaluated in cirrhotic patients with ascites undergoing paracentesis in whom volume was given IV to maintain hemodynamics. Six days after paracentesis, serum creatinine concentration had remained unchanged in the HA-treated group but had increased slightly in the DEX-treated (mean increase 0.06 mg/dL) and the gelatin-treated (mean increase 0.11 mg/dL) patients. However, differences between groups were not statistically significant

Some histological studies have shown reversible swelling of renal tubular cells after the administration of certain HES preparations, most likely related to reabsorption of macromolecules. Swelling of tubular cells causes tubular obstruction and medullary ischemia, two important risk factors for the development of ARF⁶

In patients with increased serum creatinine concentrations (>2–3 mg/dL), HES should be used cautiously. the newest, third-generation HES solution (Mw, 130 kd; DS, 0.4). Although promising results with this rapidly degradable HES preparation have been published regarding patients with moderate to severe kidney dysfunction showing no deterioration in kidney function, large, well controlled, prospective studies demonstrating no adverse effects of this HES preparations on kidney function in the critically ill are missing.^{6,7} Furthermore, although gelatin is considered a hyponcotic colloid, it too has been shown to induce hyperoncotic renal failure.⁷

Note:

1. RCT = randomized clinical trial
2. OR (Odds Ratio)

No of patients in the treatment group who experienced event/ No who did not

No of patients in the control group who experienced event/ No who did not

3. RR (Relative Risk)

No of patients in the treatment group who experienced event/ No of all patients

No of patients in the control group who experienced event/ No of all patients

- A relative risk of 1 means there is no difference in risk between the two groups.
- A RR of < 1 means the event is less likely to occur in the experimental group than in the control group.
- A RR of > 1 means the event is more likely to occur in the experimental group than in the control group.

References:

1. Roberts P. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev. 2011 Mar 16;(3)
2. Liolios A. Volume Resuscitation: The Crystalloid vs Colloid Debate Revisited. Medscape 2004
3. Carlsen S and. Pernier A Initial fluid resuscitation of patients with septic shock in the intensive care unit Acta Anaesthesiol Scand 2011; 55: 394–400
4. SAFE Study Investigators: A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004, 350:2247-2256.
5. Holbeck S, Grände PO: Effects on capillary fluid permeability and fluid exchange of albumin, dextran, gelatin, and hydroxyethyl starch in cat skeletal muscle. Crit Care Med 2000, 28:1089-1095.
6. Boldt, J, Joachim H Priebe, Intravascular Volume Replacement Therapy with Synthetic Colloids: Is There an Influence on Renal Function? Anesth Analg 2003;96:376-382
7. Honore PM et al. Hyperoncotic colloids in shock and risk of renal injury: enough evidence for a banning order? Intensive Care Med (2008) 34:2127–2129

TRANSFUSION IN TRAUMA & CRITICAL ILLNESS

Iyan Darmawan

Crystalloids (Acetated Ringer's, Lactated Ringer's and normal saline) and synthetic colloids are still the mainstay in resuscitation of hemorrhagic shock. Blood transfusion is required for severe hemorrhage. However, it is often not clear at what hemoglobin level is appropriate to trigger blood transfusion

Animal models showed that the optimum hemoglobin concentration for maintaining systemic oxygen delivery (DO_2) is 100 g/L, but in healthy human volunteers isovolemic hemodilution is tolerated at concentrations as low as 50 g/L.¹ The optimal method of resuscitation has not been clearly established. A hemoglobin level of 7–8 g/dl appears to be an appropriate threshold for transfusion in critically ill patients with no evidence of tissue hypoxia.^{2,3} However, maintaining a higher hemoglobin level of 10 g/dl is a reasonable goal in actively bleeding patients, the elderly, or individuals who are at risk for myocardial infarction. The use of blood and blood products is necessary when the estimated blood loss from hemorrhage exceeds 30% of the blood volume (class III hemorrhage).

Restrictive versus Liberal Transfusion

Results of a randomized study in critically ill patients in which hemoglobin values were maintained at a level between 10 and 12 g/dl ($n=420$), or to a restrictive strategy of transfusion, in which hemoglobin values were maintained between 7 and 9 g/dl ($n = 418$) showed that mortality at 30 days was similar for the two groups (19% versus 23%). Subgroup analysis showed that mortality rates were lower with the restrictive transfusion strategy among less acutely ill patients and among those under 55 years old. Furthermore, the mortality rate during

hospitalization was significantly lower in the restrictive strategy group (22% versus 28%)^{2,4}

Effects of Storage

Donor Blood fluidity and oxygen delivery capacity may decrease after some period of time. After 14 days of storage, there is accumulation of byproducts of glycolytic metabolism, lactic acid, and proteins.. These can result in structural and functional changes. As storage time extends past 14 days, the red cells become less pliable and therefore unable to traverse small vessels of the microcirculation, ultimately resulting in decreased oxygen delivery because the oxygenated red cells cannot traverse the end-organ capillary beds⁵ Red blood cells clearly degrade during storage. They change shape, become acidotic, lose DPG, ATP and membrane. Some break down, and others fail to circulate.^{6,7}

Dilution of coagulation factors could occur during massive transfusion. A summary of therapeutic options in massive hemorrhage as been proposed by Lier³

Some Therapeutic Options in Massive Hemorrhage	
Stabilization of concomitant factors (prevention and correction)	Targeting the core temp > 35 °C; pH > 7.2 and ionized Ca++ > 0.9 mmol/L
Improve oxygenation	pRBC to Hb 6-8g/dl, but in massive bleeding to Hct > 30% or Hb ~ 10 g/dl
Inhibit (hyper)fibrinolysis	Tranexamic acid, initial 1 g in 10 min + 1 g over 8 hr or 15-30 mg/kgBW)
Replace coagulation factors (for ongoing,severe bleeding)	FFP ≥ 20 ml/kgBW (ideally 30 ml kgBW), and Fibrinogen 4 g (aiming at > 150 mg/dl), and PCC initially 1,200-2,400 U (20-25 U/kgBW). If necessary 1-2 x FXIII 1,250 U (15-20 U/kg BW)
Platelet concentrate	2-3 U (for bleeding requiring transfusion aiming at 100,000 µL

Ratio of plasma and platelet to pRBC is important

Massive transfusion protocols with higher ratios of plasma and PLTs to pRBCs appear to be associated with improved survival in patients with massive hemorrhage⁸. For example, in trauma and labor and delivery and later for surgical and critical care patients, which provides for emergency release of 6 U of pRBCs, 4 U of plasma (liquid plasma, p24 plasma, or 5 day plasma), and 1 U of platelet. A similar 3:2 pRBC/plasma ratio was used in an MTP protocol for postpartum hemorrhage in obstetric patients. After all, fresh whole blood has been successfully utilized where component therapy is not available or has been depleted

References:

1. Moore FA, McKinley BA, Moore, EE The next generation in shock resuscitation. The Lancet Volume 363, Issue 9425, 12 June 2004, Pages 1988-1996
2. Gutierrez et al. Clinical review: Hemorrhagic shock Critical Care October 2004 Vol 8 No 5
3. Lier H Coagulation management in multiple trauma: a systematic review Intensive Care Med (2011) 37:572–582
4. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E: A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. N Engl J Med 1999, 340:409-417.
5. Marianne J Vandromme, Gerald McGwin Jr and Jordan A Weinberg* Blood transfusion in the critically ill: does storage age matter? Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine 2009, 17:35
6. Zimrin AB & JHess JR Current issues relating to the transfusion of stored red blood cells. Vox Sanguinis (2009) 96, 93–103 Blackwell Publishing Ltd
7. Zilberberg MD1 and Shorr AF Effect of a restrictive transfusion strategy on transfusion-attributable severe acute complications and costs in the US ICUs: a model simulation BMC Health Services Research 2007, 7:138
8. Pampee P Massive Transfusion Protocols for Patients With Substantial Hemorrhage. Transfus Med Rev. 2011 October ; 25(4): 293–303

VOLUME REPLACEMENT IN DHF

Budhi Santoso

The major pathophysiologic signs that distinguish DHF from Dengue fever and other febrile diseases are abnormal hemostasis and increased vascular permeability that leads to leakage of plasma. The clinical features of DHF are rather stereotyped, with acute onset of high (continuous fever) hemorrhagic diathesis (most frequently on skin), hepatomegaly, and circulatory disturbance (in most severe form as shock - dengue shock syndrome).

It is thus possible to make an early and yet accurate clinical diagnosis of DHF before the critical stage, or shock, occurs, by using the pattern of clinical presentations together with thrombocytopenia and concurrent hemoconcentration, which represent abnormal hemostasis and plasma leakage respectively.

The management of DHF is entirely symptomatic and supportive and is directed towards replacement of plasma losses for the period of 24-48 hours. Survival depends on early clinical recognition and frequent monitoring of patients for pathophysiologic changes. Early volume replacement when hematocrit rises can significantly prevent shock and/or modify disease severity ⁽¹⁾.

Studies reveal a reduction in plasma volume of more than 20% in severe cases. The evidence that supports the existence of plasma leakage includes findings of pleural effusion and ascites by examination or radiography, hemoconcentration, hypoproteinemia and serous effusion (at post mortem) ⁽²⁾.

In shock cases, satisfactory results have been obtained with the following regimen ⁽¹⁾ :

a) Immediately and rapidly replace plasma losses with isotonic salt solution and plasma or plasma expander (in cases of profound shock).

b) Continue to replace further plasma losses to maintain effective circulation for the period of 24-48 hours.

c) Correct metabolic and electrolyte disturbance (metabolic acidosis, hyponatremia, hypoglycemia or hypocalcemia).

d) Give blood transfusion in cases of significant bleeding.

Therefore, we prepare table regarding guidelines or studies stated volume replacement in DHF, as below:

No	Statement	Author/Publication
1	Monitor treatment and recovery IV resuscitation therapy ⁽³⁾ : <i>Acetated Ringer's</i> or 5% glucose (I PSS) at a rate of 10-20 ml/kg of body weight per hour (or as fast as possible). - If shock persists after 20-30 ml/kg of body weight add a plasma expander at the rate of 10-20 ml/kg per hour. - If shock persist significant internal bleeding should be suspected Continuation of intravenous therapy should be adjusted according to hematocrit and the rate should be reduced to 10 ml/kg per hour. - In general there is no need to continue the therapy beyond 48 hours.	GUIDELINES Clinical and Laboratory Guidelines for Dengue Fever and Dengue Hemorrhagic Fever/Dengue Shock Syndrome for Health Care Providers

2	Type of fluid in volume replacement in DHF ⁽⁴⁾ : ■ Crystalloid: - 5% dextrose in lactated Ringer's solution (5% D/RL) - 5% dextrose in <i>Acetated Ringer's</i> solution (5% D/RA) - 5% dextrose in half strength normal saline solution (5% D/1/2/NSS) - 5% dextrose in normal saline solution (5% D/NSS) - ■ Colloids: - Dextran 40 - Plasma -	Prevention and Control of Dengue and DHF: Comprehensive Guidelines; WHO, Regional Publication, SEARO, no. 29; New Delhi;
3	Because patients have loss of plasma (through increased vascular permeability into the serous spaces) they must be given isotonic solutions and plasma expanders, <i>such as Acetated Ringer's</i> or lactated ringer's, plasma protein fraction, and Dextran 40 ⁽⁵⁾ .	P Amin*, Sweetey Bhandare**, Ajay Srivastava*** *Consultant BHIMS, **Resident, Cook Country Hosp. Chicago. ***Resident, Bombay Hosp. Mumbai
4	In the critical stage, immediate volume replacement with isotonic solution such as normal saline (NSS), 5% D/NSS, lactated ringer's solution (RLS) or <i>Acetated Ringer's Solution (ARS)</i>, at a rate of 10-20 ml/kg/h in 1-2 hours, should be administered until circulation improves and an adequate urinary output is obtained ⁽⁶⁾ .	Faculty of Tropical Medicine, Mahidol University. All rights reserved. Webmaster : tmwww@mahidol.ac.th

5	The result of studies from various places (Bangkok, Thailand, 2000) on the use of corticosteroid in treating DSS showed no benefit either in the fatality rate or any reduction in the volume of fluid therapy or duration of therapy. Solution for volume replacement: 5% D in NSS, 5% D in 1/2 NSS, Lactated Ringer's or <i>Acetated Ringer's</i> , Plasma expander, Dextran 40 ⁽⁷⁾ .	WHO/SEARO Home© WHO Regional Office for South-East Asia 2009 All rights reserved
7	<i>Acetated Ringer's solution is a slightly hypotonic infusion fluid</i> (osmolality 270 mosmol/kg) that has inspired the belief that the fluid causes a shift of water volume to the intracellular space. In conclusion, <i>infusion of Acetated Ringer's solution does not promote cellular swelling as a result of the excretion of urine that is low in sodium</i> . A slight dehydration of fluid from the intracellular space still persisted when our measurements ended 2 h after completing the infusion ⁽⁸⁾ .	Rapid Water and Slow Sodium Excretion of Acetated Ringer's Solution Dehydrates Cells; Robert G. Hahn, MD PhD, and Dan Drobin, MD PhD Söder Hospital, S-118 83 Stockholm, Sweden

Conclusion

Isotonic crystalloids are still the mainstay of resuscitation fluid therapy in severe dengue, particularly in DSS. Starting from compensated shock isotonic crystalloid must be administered. Maintenance fluid therapy can only be given in grade 1 and grade 2 DHF when oral intake is severely compromised. Supportive fluid therapy in DHF will be discussed elsewhere in this book.

References:

1. Dengue/DHF Management of Dengue Epidemic (SEA/DEN/1): Medical and Laboratory Services and Standard Case Management of DEN/DHF/DSS During Epidemics; 2009.
2. WHO publication on Dengue Hemorrhagic Fever, chapter 3th, page:24-33.

3. Caribbean Epidemiology Center; GUIDELINES: Clinical and Laboratory Guidelines for Dengue Fever and Dengue Hemorrhagic Fever/Dengue Shock Syndrome for Health Care Providers, 2009.
4. Prevention and Control of Dengue and DHF: Comprehensive Guidelines; WHO, Regional Publication, SEARO, no. 29; New Delhi
5. Amin, P, et al; Dengue, DHF, DSS; Bombay Hospital Journal; 43003, July 2001.
6. Faculty of Tropical Medicine, Mahidol University; Knowledge on Dengue. Downloaded in 2010
7. WHO/SEARO Home © WHO Regional Office for South-East Asia 2009 All rights reserved
8. Hahn, G Robert; Drobin Dan; Rapid Water and Slow Sodium Excretion of Acetated Ringer's Solution Dehydrates Cells; Söder Hospital, S-118 83 Stockholm, Sweden

FLUID RESUSCITATION IN DIABETIC KETOACIDOSIS

Budhi Santoso

Diabetic ketoacidosis (DKA) results from absolute or relative deficiency of circulating insulin and the combined effects of increased levels of the counterregulatory hormones: catecholamines, glucagon, cortisol, and growth hormone.⁽¹⁾ They all together accelerate catabolic state with increased glucose production by the liver and kidney (via glycogenolysis and gluconeogenesis), impaired peripheral glucose utilization resulting in hyperglycemia and hyperosmolality, and increased lipolysis and ketogenesis, causing ketonemia and metabolic acidosis⁽²⁾.

The biochemical criteria for the diagnosis of DKA are⁽³⁾

- Hyperglycemia (blood glucose >11 mmol/L or > 200 mg/dL)
- Venous pH < 7.3 or bicarbonate < 15 mmol/L
- Ketonemia and ketonuria

DKA is characterized by severe depletion of water and electrolytes from both the intra and extracellular fluid (ECF) compartment, with clinical manifestations as below⁽⁴⁾:

- Dehydration
- Rapid, deep, sighing (Kussmaul respiration)
- Nausea, vomiting, and abdominal pain mimicking an acute abdomen
- Progressive obtundation and loss of consciousness
- Increased leukocyte count with left shift
- Non-specific elevation of serum amylase
- Fever only when infection is present

Death rates in DKA vary widely between published series, with death rates generally in the range of one to ten percent. Patients who are more likely to die include:

1. Have severe underlying disease (for example, acute myocardial infarction, stroke, or septic shock);
2. Have marked metabolic derangement, including profound acidosis (pH under 7.0), and marked fluid deficits;
3. With cerebral oedema (such patients are usually children, although cerebral oedema has been reported in adults) ⁽⁴⁾

On the contrary the optimal fluid management for diabetic ketoacidosis (DKA) is uncertain⁽⁵⁾ and replacement fluid in DKA is far from clear, that further research using clinically relevant outcomes should be undertaken to guide optimal management of this serious and not uncommon condition.⁽⁶⁾

The objectives of fluid and electrolyte replacement therapy are ⁽⁴⁾:

1. Restoration of circulating volume
2. Replacement of sodium and the ECF and intracellular fluid deficit of water
3. Improved glomerular filtration with enhanced clearance of glucose and ketones from the blood
4. Reduction of risk of cerebral edema

After initial 0.9% NaCl bolus. Some prefer to continue with Acetated Ringer's or Lactated Ringer's solution (8). It is important that we are realistic, 0.9% saline is not normal, but very abnormal and not remotely physiological. It inevitably causes hyperchloraemic metabolic acidosis, and it is incorrect to say that it is mild, transient and not associated with adverse outcomes. In a number of different situations "Abnormal

Saline(NaCl 0.9%)" has been shown to be inferior to physiologically balanced solutions.⁽⁸⁾

References:

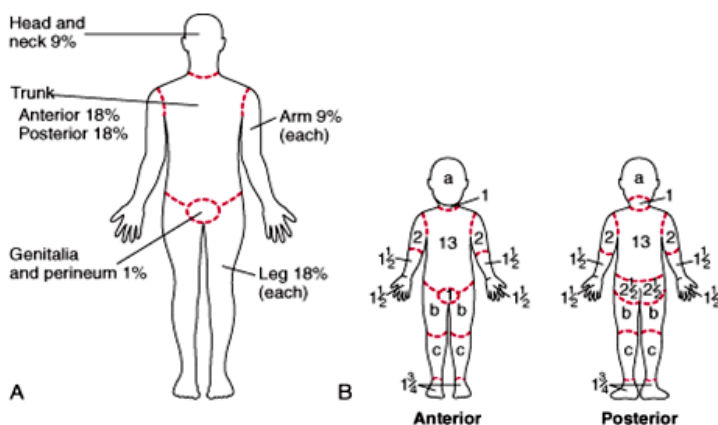
1. Wolfsdorf J et al. Diabetic ketoacidosis in children and adolescents with diabetes *Pediatric Diabetes* Volume 10, Issue s12, September 2009, Pages: 118–133
2. Kitabachi, A, Umpierrez, et al. Management of hyperglycemic crises in patients with diabetes. *Diabetes Care* 2001; 24: 131–153.
3. Dunger, DB, et al. ESPE/LWPES consensus statement on diabetic ketoacidosis in children and adolescents. *Arch Dis Child* 2004; 89:188–194.
4. Wolfsdorf J, et al. Diabetic Ketoacidosis: *Pediatric Diabetes*, 2007; 8: 28–42.
5. Eric I, et al .Improving Management of Diabetic Ketoacidosis in Children *Pediatrics* 2001;108;735.
6. Kevin J Hardy, Consultant Diabetologist, L35 5DR, Richard Griffiths, July 21th, 2007
7. Rosenbloom AL, Hanas R, Diabetic Ketoacidosis (DKA): Treatment Guidelines, *Clinical Pediatrics*, May 1996
8. Dhatariya KK. Diabetic ketoacidosis. *BMJ* 2007;334:1284-5

FLUID RESUSCITATION IN BURNS

Budhi Santoso

Burns are injuries of skin or other tissue caused by thermal, radiation, chemical, or electrical contact. Burns are classified by depth (1st-degree, superficial and deep partial-thickness, and full-thickness) and percentage of total body surface area (BSA). IV fluids are given to patients in shock or with burns > 10% BSA. A 14- to 16-gauge venous cannula is placed in 1 or 2 peripheral veins through unburned skin if possible. Venous cutdown, which has a high risk of infection, is avoided. And Patients with large burns (> 20% BSA) require fluid resuscitation ⁽¹⁾. To estimate the fluid volume needs in the first 24 h after the burn (not after presentation to the hospital) ⁽²⁾.

(A) Rule of nines (for adults) and (B) Lund-Browder chart (for children) for estimating extent of burns



Relative percentage of body surface area (% BSA) affected by growth

Body Part	Age				
	0 yr	1 yr	5 yr	10 yr	15 yr
a = 1/2 of head	9 1/2	8 1/2	6 1/2	5 1/2	4 1/2
b = 1/2 of 1 thigh	2 3/4	3 1/4	4	4 1/4	4 1/2
c = 1/2 of 1 lower leg	2 1/2	2 1/2	2 3/4	3	3 1/4

Important points regarding fluid resuscitation in Burns:

1. The goal of resuscitation of the burned patient is to provide enough fluid to maintain organ function, whilst avoiding the complications of over-resuscitation ⁽²⁾.
2. Resuscitating a burned patient is a fine balancing act, on the one hand treating the deficit of intravascular fluid and, on the other, the potential side effects of fluid overload, namely pulmonary edema, increased central venous pressure, and compartment syndrome, even in the unburned areas ⁽³⁾.
3. There was a significant difference between the volumes given the young age group, being that proportionally they received a much larger amount of volume per percent burn, and also, in the older age group, whom sustained proportionally larger burns, although they received a similar amount of volume, when compared to 15–44 years ⁽⁴⁾.
4. Excessive fluid resuscitation of large burn injuries has been associated with adverse outcomes. Experience in patients with major-burn injury to assess the relationship between fluid, clinical outcome and cause of variance from expected resuscitation volumes as defined by the Parkland formula. Although fluid resuscitation in excess of the Parkland formula was associated with several adverse events, mortality was low ⁽⁵⁾.

A recent multi-centre study found that resuscitation > 5 mL/kg/% TBSA significantly increased the odds of pneumonia and death with an overall mortality of 25% ⁽⁶⁾.

The use of acetated ringer's solution in burn:

- Acetated ringer's is often used for fluid resuscitation after a blood loss due to trauma, surgery, or a burn injury ⁽⁷⁾

- Acetated ringer's is used for fluid resuscitation especially in hemorrhagic shock without increasing the risk of lactic acidosis ⁽⁸⁾
- Acetated ringer's and LR could maintain the 24 hours "survival rate" in severe burn (guinea pig) compare to NS (100% & 87%). And after 24 hours acetated ringer's still had beneficial effect significantly compare to LR, in term of ⁽⁹⁾⁽¹⁰⁾ :
 - minimizing the risk of lactic acidosis
 - highest ability in converting to bicarbonate (2.5 – 4 times rapidly)
 - determining as a physiologic fuel for heart cells

Conventional Parkland formula vs decreased fluid volume ⁽¹¹⁾

The amount of crystalloid fluid volume based on Parkland formula was 4 ml/kg/% Burn, with half this volume given in first 8 hours.

The impact of decreased fluid resuscitation on multiple-organ dysfunction after severe burns has been evaluated. This approach was referred to as "permissive hypovolemia".

Methods

Two cohorts of patients with burns >20% BSA without associated injuries and admitted to ICU within 6 h from the thermal injury were compared. Patients were matched for both age and burn severity. The multiple-organ dysfunction score (MODS) by Marshall was calculated for 10 days after ICU admission. Permissive hypovolemia was administered by a hemodynamic-oriented approach throughout the first 24-h period. Hemodynamic variables, arterial blood lactates and net fluid balance were obtained throughout the first 48 h.

Results

Twenty-four patients were enrolled: twelve of them received the Parkland Formula while twelve were resuscitated according to the permissive hypovolemic approach. Permissive hypovolemia allowed for less volume infusion (3.2 ± 0.7 ml/kg/% burn versus 4.6 ± 0.3 ml/kg/% burn; $P < 0.001$), a reduced positive fluid balance ($+7.5 \pm 5.4$ l/day versus $+12 \pm 4.7$ l/day; $P < 0.05$) and significantly lesser MODS Score values ($P = 0.003$) than the Parkland Formula. Both hemodynamic variables and arterial blood lactate levels were comparable between the patient cohorts throughout the resuscitation period.

Conclusions

Permissive hypovolemia seems safe and well tolerated by burn patients. Moreover, it seems effective in reducing multiple-organ dysfunction as induced by edema fluid accumulation and inadequate O_2 tissue utilization.

References:

1. Wolf SE Burn: Last full review, revision March 2009; Retrieved January 2012 from http://www.merck.com/mmpe/sec21/ch315/ch315a.html#S21_CH315_F00..
2. Oliver, RI, Spain D., & Stadelmann, W. (2006). Burns, Resuscitation and early management. Retrieved 15 January 2012 from <http://emedicine.medscape.com/article/1277360-overview>
3. Fodor, L & Fodor, A, et al; Controversies in fluid resuscitation for burn management: Literature review and our experience, Int. J. Care Injured (2006) 37, 374—379;
4. S. Piccolo-Daher et al.. Acute burn intravenous resuscitation—Are we giving too much volume to our patients? Burns, Volume 33, Issue 1, Page S155
5. Dulhunty JM, Boots RJ, Rudd MJ, Muller MJ, Lipman J. Increased fluid resuscitation can lead to adverse outcomes in major-burn injured patients, but low mortality is achievable. Burns. 2008;34(8):1090–1097 Klein MB,

Hayden D, Elson C, Nathens AB, Gamelli RL, Gibran NS, et al. The association between fluid administration and outcome following major burn: a multicenter study. *Ann Surg* 2007;245:622–8

6. www.medic8.com © Medic8 ® All Rights Reserved Retrieved 15 January 2012
7. Kveim M, et al. Utilization of exogenous acetate during canine hemorrhagic shock. *Scand J Clin Lab Invest* 1979; 39 : 653 - 8.
8. Conahan ST, et al. Resuscitation Fluid Composition and Myocardial Performance during Burn Shock. *Circ Shock* 1987; 23(1): 37-49.
9. Osuka Pharmaceuticals. Ringer Acetate Solution in Clinical Practice. MediMedia Com; 1-5, 1999.
10. S. Arlati, E. Storti, V. Pradella, L. Bucci, A. Vitolo, M. Pulici. Decreased fluid volume to reduce organ damage: A new approach to burn shock resuscitation? A preliminary study *Resuscitation*, Volume 72, Issue 3, March 2007, Pages 371-378

REFERENCES ON THE USE OF ACETATED RINGER'S IN BURNS

Budhi Santoso

Besides LR and NS, Acetated Ringer's (AR) was already known as crystalloid infusion for replacement fluid for resuscitation (gastroenteritis with severe dehydration, hemorrhagic shock, DSS), also for intraoperative, priming solution for cardiopulmonary bypass (CPB) and replacement during acute stroke also for burn patients⁽¹⁾. If we traceback regarding the infuse history, in 1885, Ringer's solution was invented by Ringer, and, 47 years later, Hartmann modified it by adding sodium lactate, with the idea of combating acidosis in patients⁽²⁾. The current Ringer's lactate solution in use has been developed on the basis of Hartman's solution. In 1949, Mudge et al. showed that acetate sodium was a rapidly available non-toxic fixed base source suitable for parenteral administration when alkalinization is indicated in humans⁽³⁾. In 1952, Fox et al. used a balanced electrolyte solution containing acetate sodium and citrate to provide bicarbonate ions to postoperative patients⁽⁴⁾.

Concerning the fluid resuscitation strategy in an extensively burned patient RL has been predominantly used as a buffer agent to maintain the pH of body fluid rather than RA since the report by Baxter et al. in 1968⁽⁵⁾. And there has been debate for over 60 years on the volume and sodium content, role of anions, toxicity of the fluid, and effectiveness of colloids. Eventhough recent studies have demonstrated that RA administration may improve metabolic acidosis faster than RL, increase the energy level in peripheral tissue, decrease metabolic stress in the liver, exhibit a more potent vascular dilatation effect than lactate, and maintain the core temperature⁽⁶⁾.

Herewith are compiled references regarding AR in burn patients:

1. Conahan et al. showed that RA resuscitation resulted in a significant improvement regarding cardiac output and contractility, the ATP content of the heart, and 48-h survival compared to RL resuscitation in guinea pigs with third-degree burns totaling 35–40% of TBSA⁽⁷⁾.
2. Venkatesh et al. observed progressive dysoxia in the splanchnic region as well as in normal and burnt skin in seven patients with major burns⁽⁸⁾.
3. Katsunori Aoki et al.⁽⁶⁾ recently reported the effects of Ringer's lactate (RL) and acetate (RA) solutions on parameters of splanchnic dysoxia such as PgCO₂ (PCO₂ of gastric mucosa) and pHi (pH of gastric mucosa) using a gastric tonometer, in addition to blood markers such as the serum arterial level of lactate, base excess, ketone body ratio, and antithrombin during the first 72 h of the resuscitation period in patients with burns covering 30% or more of their body surface. A prospective study was conducted in the university tertiary referral centers. There were no significant differences in the average age,

TBSA (total burn surface area), and resuscitative fluid volume during the first and second 24 h between the two groups. In the RA group, PCO₂ gap values calculated employing the formula: PgCO₂ - PaCO₂ (arterial PCO₂), and pH gap calculated by: pHa (arterial pH) - pHi, improved to the normal ranges at 24 h post burn, which was significantly faster than in the RL group. On the other hand, there were no significant differences in blood parameters between the two groups over the course. These results suggest that fluid resuscitation with RA may more rapidly ameliorate splanchnic dysoxia, as evidenced by gastric tonometry, compared to that with RL⁽⁶⁾.

References:

1. Darmawan, I; Acetated Ringer's additional usages; Proceeding from Asering symposia in ISOA/ISROA, gran Melia Hotel, Jakarta; 2002;
2. JA. Sydney Ringer (1834–1910) and Alexis Hartmann (1898–1964). *Anesthesia* 1981;36:1115–21.
3. Mudge GH, Manning JA, Gilman A. Sodium acetate as a source of fixed base. *Proc Soc Exp Biol Med* 1949;71:136–8.
4. Fox Jr CL, Winfield JM, Slobody LB, Swindler CM, Lattimer JK. Electrolyte solution approximating plasma concentrations with increased potassium for routine fluid and electrolyte replacement. *J Am Med Assoc* 1952;148:827–33.
5. Baxter CR, Shires T. Physiological response to crystalloid resuscitation of severe burns. *Ann N Y Acad Sci* 1968;150:874–94.
6. Katsunori Aoki, et al; A comparison of Ringer's lactate and acetate solutions and resuscitative effects on splanchnic dysoxia in patients with extensive burns: *BURNS* 36 (2010) 1080–1085
7. Conahan ST, Dupre A, Giaimo ME, Fowler CA, Torres CS, Miller HI. Resuscitation fluid composition and myocardial performance during burn shock. *Circ Shock* 1987;23: 37–49.
8. Venkatesh B, Meacher R, Muller MJ, Morgan TJ, Fraser J. Monitoring tissue oxygenation during resuscitation of major burns. *J Trauma* 2001;50:495–9.

SEVERE MALARIA AMONG CHILDREN

(Fluid Consideration)

Budhi Santoso

Half of the world's population is at risk from malaria. Each year almost 250 million cases occur, causing 860 000 deaths. Approximately 85% of these deaths are among children, and most occur in Africa ⁽¹⁾. Many of the clinical features of severe malaria occur in children. The commonest and most important complications of *Plasmodium falciparum* infection in children are: cerebral malaria, severe anemia, respiratory distress and hypoglycemia ⁽²⁾. Shock in severe malaria carries a high mortality in children. It should be treated initially with oxygen and fluids (with monitoring of central venous pressure if available). It is unclear how aggressive the volume expansion should be in terms of safety and effectiveness. Massive hemorrhage, from the gastrointestinal tract or rarely a ruptured spleen, should be excluded. A septic screen including blood cultures should be performed and appropriate broad-spectrum antibiotics administered to cover the possibility of bacterial sepsis.

Key aspects

Key aspects of the initial assessment of children with severe malaria are: level of consciousness (coma scale for children), rate and depth of respiration, presence of anemia, pulse rate and blood pressure, state of hydration, temperature.

Fluid resuscitation

The role of aggressive fluid resuscitation in the management of severe malaria, particularly in children, is unclear and currently controversial. The debate centers around whether hypovolemia plays an important role in the pathophysiology of severe malaria, causing poor tissue perfusion, leading to anaerobic glycolysis and

consequent acidosis ^(2,3). Advocates of aggressive fluid repletion suggest that the standards of care applied in resource-rich settings for severely ill children with bacterial sepsis should be extrapolated to severe malaria, while those against argue that there is no evidence that severe dehydration occurs in severe malaria and are concerned that overzealous rehydration may lead to pulmonary and cerebral edema. So rate of infusion of I.V. fluids should be carefully monitored, as should the urine production ⁽⁴⁾.

Acidosis

Metabolic acidosis, a common complication of severe malaria, is strongly associated with fatal outcome in children. Lactic acid is an important contributor, but impaired renal bicarbonate handling and the presence of other as yet unidentified acids also play major roles. Dichloroacetate (which stimulates pyruvate dehydrogenase) has been shown to reduce plasma lactate in severe malaria. Hemofiltration has been shown to rapidly eliminate acidosis in malaria patients with renal failure, even in the presence of lactic acidosis. Early hemofiltration may be a useful strategy in patients with acidosis and renal impairment who have not yet developed established renal failure, but this has not yet been evaluated in a clinical trial. Asering[®] is used for fluid resuscitation especially in hemorrhagic shock without increasing the risk of lactic acidosis and metabolized mainly in muscle ^(5,6)

Anemia

This is present in almost all patients with severe malaria but occurs most prominently in young children. Benefits of blood transfusion should outweigh the risks (especially of HIV and other pathogens). There is no clear evidence supporting specific hemoglobin cut-off levels, and a number of figures are quoted in reviews and guidelines. In adults, the threshold for blood

transfusion is commonly set at a hematocrit < 20%. Clinical evidence (Kenya) has led to threshold hemoglobin levels for African children of 5 g/dL if there is co-existing respiratory distress, impaired consciousness, or hyperparasitemia or at an absolute cut-off of 4 g/dL. ⁽⁴⁾

ARDS

This feared complication has a high mortality rate and can develop several days after admission and onset of treatment. Clinical research is needed into both the pathophysiology and treatment of this condition. The etiology is poorly understood, and treatment in malaria is currently based on expert opinion and extrapolation from studies on ARDS associated with other conditions.

Medical Treatment

WHO Guidelines for children in high-transmission areas, the following antimalarial medicines are recommended as there is insufficient evidence to recommend any of these antimalarial medicines over another for severe malaria ⁽⁷⁾:

- Artesunate 2.4 mg/kg bw i.v. or i.m. given on admission, then at 12 h and 24 h, then once a day;
- Artemether 3.2 mg/kg bw i.m. given on admission then 1.6 mg/kg bw per day;
- Quinine 20 mg salt/kg bw on admission (i.v. infusion or divided i.m. injection), then 10 mg/kg bw every 8 h; infusion rate should not exceed 5 mg salt/kg bw per hour.

If inotropes are necessary, dopamine has been used safely in malaria, and dobutamine and norepinephrine may also be used though there is little experience with them in severe malaria. Epinephrine should be avoided as it induces serious lactic acidosis.

Conclusion:

Besides antimalarial, the fluid consideration in severe malaria among children seems still debatable. Thus clinician should emphasized patients with cautiously and holistic, as below:

- To correct hypovolemic shock with acidosis firstly give the fluid resuscitation (aggressive or not aggressive in terms of safety and effectiveness still debatable). Dichloroacetate (which stimulates pyruvate dehydrogenase) has been shown to reduce plasma lactate in severe malaria (Acetated Ringer's is used for fluid resuscitation especially in hemorrhagic shock without increasing the risk of lactic acidosis and mainly metabolized in muscle ^(5,6)).
- To meet the need provision of water and electrolytes based on normal daily requirement give the maintenance fluid.
- Other complications such: Anemia should be managed properly.

References

1. Hommel M and Gilleeds HM. Malaria. In Topley and Wilson's Microbiology and Microbial Infections Published Online : 15 MAR 2010. Retrieved 15 January 2012
2. Day N, Dondorp AM; Management of Patients with Severe Malaria; Am. J. Trop. Med. Hyg., 77(Suppl 6), 2007, pp. 29–35 Copyright © 2007
3. Kveim M, et al. Utilization of exogenous acetate during canine hemorrhagic shock. Scand J Clin Lab Invest 1979; 39 : 653 - 8.
4. Maxwell MH, Kleeman CR, Narins RG. Clinical Disorders of Fluid and Electrolyte Metabolism. MacGraw-Hill 1987 4th edition p 1063
5. Newman, Robert.MD; The WHO Global Malaria Programme (GMP); WHO releases new malaria guidelines for treatment and procurement of medicines; 2008

ACETATED RINGER'S SOLUTION HAS BENEFICIAL EFFECT IN CARDIAC SURGERY

Iyan Darmawan

Introduction

All colloid solutions have negative effects on blood coagulation, but these effects are dependent on the dose and type of fluid administered^{1,2,3}. Since cardiopulmonary bypass increases the risk of postoperative bleeding, the authors examined to what extent various doses of rapidly degradable hydroxyethyl starch (HES) or gelatin, in comparison with Acetated ringer's, impaired whole blood coagulation after cardiac surgery.

Schramko et al^{4,5} compared the effects of two colloids and acetated Ringer's solution on blood coagulation after cardiac surgery. Forty-five patients received three relatively rapid boluses (each 7 ml/kg) of either 6% HES (130/0.4) ($n = 15$), 4% gelatin ($n = 15$), or Acetated ringer's ($n = 15$) after elective cardiac surgery to maintain optimal intravascular volume. The study solution was continued as an infusion (7 ml/kg) for the following 12 hours. The total cumulative dose of the study solution was 28 ml/kg. If signs of hypovolemia were observed, Acetated ringer's was given. Blood coagulation was assessed by thromboelastometry (ROTEM).

Clot formation time was prolonged after infusion of 7 ml/kg both colloid solutions ($P < 0.05$). Delayed clot formation and impaired clot strength, still deteriorated after the cumulative doses of 14 ml/kg and 21 ml/kg colloids ($P < 0.05$). In contrast, after infusion of 14 ml/kg and 21 ml/kg Acetated ringer's clot strength increased

slightly but significantly. Some signs of disturbed coagulation were seen in the gelatin group on the first postoperative morning: MCF and the α angle were still decreased in comparison with the Ringer group ($P < 0.05$). Signs of excessive fibrinolysis were not observed. Chest tube output was comparable between all groups. No clinical thromboses were observed.

Conclusion

HES (130/0.4) 7 ml/kg or gelatin impaired clot formation and firmness shortly after cardiac surgery. This effect became more pronounced as the dose increased. On the contrary, Acetated ringer's has better profile because it increased blood coagulation capacity slightly.

References:

1. Niemi T, et al.: Gelatin and hydroxyethyl starch, but not albumin, impair hemostasis after cardiac surgery. *Anesth Analg* 2006, 102:998-1006.
2. Linden P, et al.: The effects of colloid solutions on hemostasis. *Can J Anaesth* 2006, 53:30-39.
3. Cope JT et al. Intraoperative Hetastarch Infusion Impairs Hemostasis After Cardiac Operations *The Annals of Thoracic Surgery*, Volume 63, Issue 1, January 1997, Pages 78-82
4. Schramko A et al Hydroxyethyl starch or gelatin impairs, but Acetated ringer's enhances, coagulation capacity dose dependently after cardiac surgery. *Critical Care* 2009, 13(Suppl 1)
5. Schramko A, et al. Hydroxyethylstarch and gelatin solutions impair blood coagulation after cardiac surgery: a prospective randomized trial. *British Journal of Anaesthesia* 104 (6): 691-7 (2010)

THE EFFECT OF ACETATED RINGER'S SOLUTION IN MAINTAINING CORE TEMPERATURE OF SURGICAL PATIENTS

Iyan Darmawan

Introduction

Hypothermia is defined as a core temperature less than 36°C (96.8°F). Shivering is involuntary and repeated muscle activity (trembling) to increase heat production. Shivering occurs when the temperature at the preoptic region of hypothalamus is lower than surface temperature¹

Mild hypothermia is likely to protect some patients, but it surely harms others. During cardiac surgery the core temperature is often intentionally reduced to approximately 28°C in order to protect the myocardium and central nervous system.² However, in other general surgeries, even mild hypothermia reduces resistance to surgical-wound infection by directly impairing immune function (especially oxidative killing by neutrophils) and decreasing the cutaneous blood flow, which reduces the delivery of oxygen to tissue. Perioperative hypothermia is also associated with protein wasting and the decreased synthesis of collagen. Together, these factors triple the incidence of surgical-wound infection and increase the duration of hospitalization by approximately 20 percent in patients who become hypothermic during elective colon resection.³

Mild hypothermia also reduces platelet function and decreases the activation of the coagulation cascade. In a finding consistent with these data from in vitro studies, hypothermia significantly increased the loss of blood and the need for allogeneic transfusion during elective primary hip arthroplasty. Core hypothermia of just 1.5°C triples the incidence of ventricular tachycardia and

morbid cardiac events. Interestingly, the cardiac events involved appear to be unrelated to shivering after anesthesia, which suggests that factors other than increased metabolic rate are more important.

Mild hypothermia decreases the metabolism of most drugs, including propofol and the muscle relaxants vecuronium and atracurium. Consistent with this decreased metabolism is the observation that mild hypothermia significantly prolongs the postoperative recovery period (even if temperature is not a discharge criterion). Shivering occurs in approximately 40 percent of unwarmed patients who are recovering from general anesthesia and is associated with substantial adrenergic activation and discomfort. Some patients report the discomfort of postoperative shivering and the sensation of cold to be even worse than surgical pain. Despite the well-documented adverse effects of mild hypothermia, there is no evidence of any benefits associated with the perioperative maintenance of supranormal core temperatures (i.e., 38°C or 39°C).³

Regional anesthesia impairs both central and peripheral thermoregulation. As a result, hypothermia is common in patients given spinal or epidural anesthetics. Patients who become sufficiently hypothermic may start to shiver

Use of Acetated Ringer's solution has been associated with maintenance of core body temperature after isoluran and sevofluran general anesthesia, better than Ringer's lactate.⁴ Following induction with 5 mg/kg of thiamylal and 0.1 mg/kg of vecuronium, patients were randomly assigned to one of four groups (15 patients per group). They received inhalation anesthetics (66% nitrous oxide [N₂O] and 1.0% to 2.0% isoflurane or 1.3% to 2.6% sevoflurane) and LR or AR. Tympanic membrane temperatures in the patients given AR were significantly higher than those given LR during isoflurane anesthesia 5 and 30 minutes after induction of anesthesia.

Preliminary study by Chandra S, et al ⁵ comparing the effects of acetated Ringer's (Asering) and lactated Ringer's solution on core temperature and the frequency of shivering in 40 patients with caesarean section under subarachnoid anesthesia demonstrated that acetated ringer's is more effective in preventing hypothermia and postoperative shivering compared to lactated ringer's solution.

References:

1. Clinical guideline for the prevention of unplanned perioperative hypothermia. *J Perianesth Nurs* 2001 Oct;16(5):305-14.
2. Hindman BJ, et al. Mild Hypothermia as a Protective Therapy during Intracranial Aneurysm Surgery: A Randomized Prospective Pilot Trial *Neurosurgery*: January 1999 - Volume 44 - Issue 1 - pp 23-32
3. Sessler D.I. Mild Perioperative Hypothermia. *NEJM*. Vol 336:1730-1737. 1997
4. Kashimoto S, et al Comparative effects of Ringer's acetate and lactate solutions on intraoperative central and peripheral temperatures. *J Clin Anesth* 1998 Feb;10(1):23-7
5. Chandra S, Harijanto E, Bram. Comparative Effects of Ringer's Acetate (Asering) and Ringer's Lactate on core temperature and the frequency of shivering in Caesarean Section under Subarachnoid Anesthesia. *International Symposium on Obstetric Anesthesia*, 2006

HYPONATREMIA

Iyan Darmawan

Introduction:

Sodium ion (Na^+) is the main cation in extracellular compartment (plasma and interstitial). Normal serum sodium concentration ranges from 135 -145 mmol/L. Na^+ has major role in regulating plasma osmolality. Hyponatremia was reported in up to 28% of patients undergoing acute hospital care and 21% of patients undergoing ambulatory care.¹ Elderly patients, and those with certain conditions such as heart failure, tuberculosis, cirrhosis, and head injury, maybe at increased risk for hyponatremia

Both extremely low and high concentration can impair brain function. For example, severe hyponatremia (< 115 mmol/L) can result in neurologic disturbances, such as reduced consciousness, coma and seizures.^{2,3} Often serious complications can arise not only from the disorder itself but also from errors in management. Aggressive management leads to complications and death..

Some important points to note before correcting hyponatremia^{3,4,5} :

- There is no consensus about the optimal treatment of symptomatic hyponatremia.
- Less serious symptoms usually require only water restriction and close observation.
- Severe symptoms (e.g., seizures or coma) requires hypertonic saline (3% NaCl which contains 513 mmol of Na^+ per L)
- Most hyponatremic patients with hypovolemia can be treated successfully with isotonic saline (containing 154 mmol Na^+ /L)
- Seizures induced by hyponatremia can be stopped by rapid increases in the serum sodium

concentration that average only 3 to 7 mmol per liter

- Most reported cases of osmotic demyelination occurred after rates of correction that exceeded 12 mmol per liter per day were used,
- But isolated cases occurred after corrections of only 9 to 10 mmol per liter in 24 hours or 19 mmol per liter in 48
- Some experts recommend a targeted rate of correction that does not exceed 8 mmol per liter on any day of treatment..
- However, the initial rate of correction can still be 1 to 2 mmol per liter per hour for several hours in patients with severe symptoms.
- Recommended indications for stopping the rapid correction of symptomatic hyponatremia (regardless of the method used) are the cessation of life-threatening manifestations, moderation of other symptoms, or the achievement of a serum sodium concentration of 125 to 130 mmol per liter (or even lower if the base-line serum is below 100 mmol/L)

HOW TO CORRECT:

- Irrespective of the etiology, severe hyponatremia must be corrected by hypertonic saline (3% NaCl 3%) if there is neurological symptom, such as reduced consciousness or seizures. There is no strong reason to administer 3% NaCl to asymptomatic hyponatremia (or conc > 125 mEq). In principle 1 L of sodium containing solution will increase or decrease plasma Na^+ concentration
- The magnitude of change of plasma Na^+ concentration can be calculated with the formula:

$$\frac{\text{Infusate Na}^+ - \text{serum Na}^+}{\text{Total body water} + 1}$$

6. Total body water in adults is 60% of body weight, whereas in children 70% of body weight

CASE ILLUSTRATION:

A 30-year-old woman sustained three grandmal seizures, two days after an appendectomy.

She received 20 mg of diazepam and 250 mg of phenitoin intravenously and underwent laryngeal intubation with mechanical ventilation.

Allo-anamnesis to nurse reveals that during first day after surgery, patient had been infused with 2 liters of 5% dextrose and 1 liter of lactate ringer's solution. Subsequently she was allowed to drink.

Clinically patient was not dehydrated and weighed 46 kg. She was stuporous and responded only to pains and not to commands.

Lab: Plasma Na^+ 112 mmol/L, plasma osmolality 228 mOsm/kg, urine osmolality 510 mOsm/kg
WD/ hypotonic hyponatremia due to water excess.

Planned treatment to correct Na^+ in the first 5 hours to reach 117 mmol/L, hoping that seizures stop. Subsequently, followed by increasing by 5 mmol/L for 19-20 hours afterwards. What are the amount and rate of administration of 3% NaCl 3% required?

$$\frac{\text{Infusate } \text{Na}^+ \text{ infus} - \text{Serum } \text{Na}^+}{\text{Total body water} + 1}$$

$$\frac{513 - 112}{60\% \text{BB} + 1} =$$

$$\frac{401}{(60\% \times 46) + 1} =$$

$$\frac{401}{28.6} = 14.02$$

Meaning 1 L of 3% NaCl will raise plasma Na^+ by approx. 14 mmol/L

Within the first 5 hours it was planned to raise Na^+ concentration by 5 mmol/L, thus required only: $5 : 14 = \pm 0.357$ L of 3% NaCl 3% or 357 ml. Therefore rate of administration is $357 : 5 = \pm 72$ ml per hour or 18 drops per minute (using Otsuka infusion set).

After 5 hours, Na^+ concentration rose to 117 mmol/L. Seizures stopped and patient was still somnolent. Next, it was planned to increase plasma Na^+ concentration by 5 mmol over 19-20 hours. Rate of administration is $357 : 19 = \text{approx } 18$ ml/hours. It is common to administer such slow rate of infusion by use of infusion pump. Maintenance fluid requirement should be fulfilled with normal saline, the amount of which should be restricted in this patient. 3% NaCl 3% is discontinued after plasma Na^+ reaches 125 or 130 mmol/L.

Clinicians can choose to target desired plasma Na^+ concentration within specific time range (no consensus) and could simply modify based on individual response. It is most important to avoid aggressive correction.

References :

1. Haskal R. Current issues for nurse practitioners: Hyponatremia Journal of the American Academy of Nurse Practitioners 19 (2007) 563–579
2. Halawa Y. Hyponatremia and risk of seizures: A retrospective cross-sectional study Epilepsia, 52(2):410–413, 2011
3. Adrogue, HJ; and Madias, NE. Primary Care: Hyponatremia. New England Journal of Medicine 2000; 342(21):1581-1589.
4. Banks CJ & Furyk JS. Review article: Hypertonic saline use in the emergency department Emergency Medicine Australasia (2008) 20, 294–305
5. Overgaard-Steensen C. Initial approach to the hyponatremic patient Acta Anaesthesiol Scand 2011; 55: 139–14

HYPONATREMIA IN HEART FAILURE

Iyan Darmawan

Introduction

Hyponatremia (plasma sodium < 135 mEq/L) is a common finding in heart failure. It is associated with a poor prognosis. Symptomatic patients are usually managed by fluid restriction that results in a negative water balance, increases in plasma osmolality, and increases in plasma sodium.⁽¹⁾ Unfortunately, this therapy is not very effective and may cause patient's discomfort. Combination of hypertonic saline (eg NaCl 3%) and loop diuretics is often added to fluid restriction, but this over aggressive approach has been associated with abrupt increase in plasma sodium concentration leading to CNS demyelination. Moreover, Furosemide administration is, in fact, associated with potentially lethal electrolyte abnormalities, neurohormonal activation, worsening renal function, and lastly, resistance to its administration.⁽²⁾ In current practice, there is a tendency to view hyponatremia as dilutional effect from fluid accumulation, but no integrated approach is taken to manage it. However, only recently a novel therapeutic modality has been developed to cope with hyponatremia while simultaneously improve hemodynamic status and prognosis of patients with heart failure.⁽³⁾

Why does hyponatremia occur in heart failure?

Hypervolemic Hyponatremia in heart failure originates from reduced cardiac output and blood pressure, which stimulates vasopressin, catecholamine, and the renin-angiotensin-aldosterone axis. Increased vasopressin levels have been reported in patients with impaired left ventricular function before the onset of symptomatic heart failure.^(4,5) In patients with worsening HF, decreased stimulation of mechanoreceptors in the left ventricle, carotid sinus, aortic arch, and renal afferent

arterioles leads to increased sympathetic discharge, activation of the renin-angiotensin-aldosterone system, and nonosmotic release of vasopressin among other neurohormones.⁽¹⁾ Despite increased total fluid volume, increased sympathetic drive contributes to avoid sodium and water retention, and the enhanced vasopressin release results in an increased number of aquaporin water channels in the collecting duct of the kidney that promote abnormal free water retention and contribute to the development of hypervolemic hyponatremia.

Vasopressin a new target for the treatment of heart failure

Initially, vasopressin was named for its pressor effect but, as more information surfaced and its major role in water balance emerged, its name has been interchanged with antidiuretic hormone. Vasopressin receptors have diverse physiological actions on liver, smooth muscle, myocardium, platelets, brain and kidney ⁽⁶⁾

There are three receptor subtypes of AVP (arginine vasopressin) ^(7,8) as shown below:

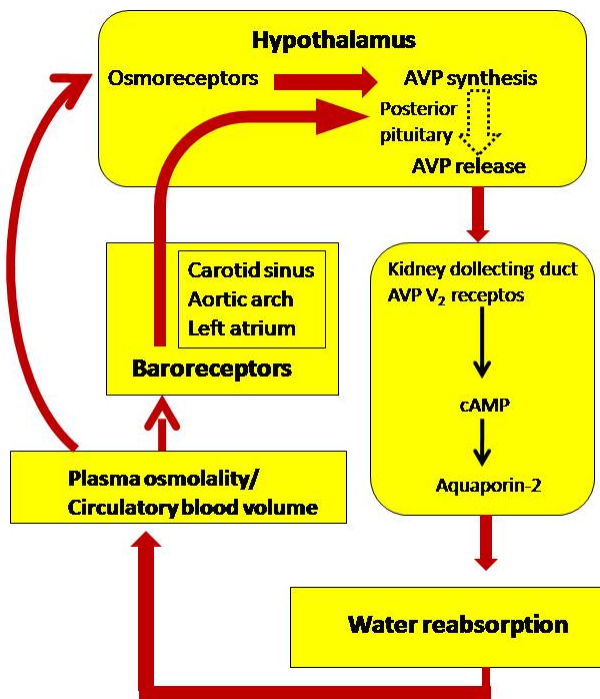
Receptor subtypes	Site of action	AVP activation effects
V _{1a}	Vascular smooth muscle cells Platelets Lymphocytes and monocytes Adrenal cortex	Vasoconstriction Platelet aggregation Coagulation factor release Glycogenolysis
V _{1b}	Anterior pituitary	ACTH and β -endorphin release
V ₂	Renal collecting duct principal cells	Free water reabsorption

Physiological actions of AVP ⁽⁷⁾

Through activation of its V1a and V2 receptors, AVP has demonstrated to play an integral role in various physiological processes, including body fluid regulation, vascular tone regulation and cardiovascular contractility. V1a receptors are located on both vascular smooth muscle cells and cardiomyocytes, and have been shown to modulate blood vessel vasoconstriction and myocardial function. V2 receptors are located on renal collecting duct principal cells, which are coupled to aquaporine water channels and regulate volume status through stimulation of free water and urea reabsorption.

The primary function of AVP, or formerly known as antidiuretic hormone (ADH), is to regulate water and solute excretion by the kidney. AVP plays a significant role in volume homeostasis under normal physiological conditions through continuous response to changes in plasma tonicity. When plasma tonicity changes by as little as 1%, osmoreceptor cells located in the hypothalamus undergo changes in volume and subsequently stimulate neurons of the supraoptic and paraventricular nuclei. Based upon the degree of tonicity change, activation of these neurons modulates the degree of AVP secretion from the axon terminals of the posterior pituitary. After release into the circulation, AVP binds to V2 receptors located on collecting duct principal cells in the kidney.

This binding activates a guanine nucleotide binding protein (Gs) which in turn activates adenylate cyclase, subsequently increasing intracellular cyclic-3',5'-adenosine monophosphate (cAMP) synthesis. The generated cAMP then activates protein kinase A (PKA), which stimulates the synthesis of aquaporin-2 (AQ2) water channel proteins and their shuttling to the apical surface of the collecting duct. These channels allow free water to be reabsorbed across the apical membrane of the collecting duct, via the renal medullary osmotic



gradient, for ultimate return to the intravascular circulation. Thus, AVP secretion alters collecting duct permeability, increases free water reabsorption, and ultimately decreases plasma osmolality. In healthy individuals, when plasma becomes hypertonic (> 145 mEq/L of serum sodium), plasma AVP concentrations exceed 5.0 pg/mL and urine becomes maximally concentrated (1200 mOsm/kg water) in the collecting duct of the nephron. Conversely, when plasma becomes hypotonic (< 135 mEq/L of serum sodium), plasma AVP concentrations are undetectable and the urine remains maximally dilute (minimum of 50 mOsm/kg water) as it is excreted. Under isotonic conditions, AVP is secreted to an intermediate plasma concentration of 2.5 pg/mL, subsequently producing a urine osmolality approximating 600 mOsm/kg water.

Vascular tone regulation

In addition to its renal effects on the V2 receptor inresponse to changes in plasma osmolality, AVP also maintains and regulates vascular tone via V1a receptors located on vascular smooth muscle cells. AVP release is stimulated when cardiopulmonary and sinoaortic baroreceptors detect reductions in pressure, such as during dehydration, profound hypotension or shock.

Conversely, detectable increases in pressure by these baroreceptors leads to a reduction in the production and release of AVP. In response to minor decreases in arterial, venous and intracardiac pressure, stimulation of the V1a receptors by AVP results in potent arteriole vasoconstriction with significant increases in systemic vascular resistance (SVR). In healthy individuals, however, physiological increases in AVP release do not usually produce significant increases in blood pressure, since AVP also potentiates the sinoaortic baroreceptor reflex in response to elevated SVR. Augmentation of the baroreceptor reflex, which is mediated through V2 receptor stimulation, subsequently lowers both heart rate and cardiac output to maintain constant blood pressure. Thus, in normal individuals, AVP release increases SVR without increasing blood pressure via stimulation of both V1a and V2 receptors. Blood pressure changes become detectable only when supraphysiological AVP concentrations are attained, and V1a -activated increases in SVR outweigh the V2-activated potentiation of the baroreceptor reflex.

VP dysregulation ⁽⁸⁾

Arginine vasopressin (AVP) plays a central role in the regulation of water and electrolyte balance. Dysregulation of AVP secretion, along with stimulation of AVP V2 receptors, is responsible for hyponatremia (serum sodium concentration < 135 mEq/L) in congestive heart failure (CHF). The stimulation of atrial and arterial baroreceptors in response to hypotension

and volume depletion results in the nonosmotic release of AVP. The predominance of nonosmotic AVP secretion over osmotic AVP release plays a key role in the development of water imbalance and hyponatremia in CHF and other edematous disorders. The AVP-receptor antagonists are a new class of agents that block the effects of AVP directly at V2 receptors in the renal collecting ducts. AVP-receptor antagonism produces aquaresis, the electrolyte-sparing excretion of water, thereby allowing specific correction of water and sodium imbalance. This review summarizes recent data from clinical trials evaluating the efficacy and safety of these promising agents for the treatment of hyponatremia

Acute Hemodynamic Effects of V₂ receptor blocker

In 181 patients with advanced HF, Tolvaptan a vasopressin V2 receptor antagonist was studied in randomized double-blind treatment. Patients were randomized to tolvaptan single oral dose (15,30 or 60 mg) or placebo ⁽³⁾

Tolvaptan at all doses significantly reduced pulmonary capillary wedge pressure (-6.4 ± 4.1 mm Hg, -5.7 ± 4.6 mm Hg, -5.7 ± 4.3 mm Hg, and -4.2 ± 4.6 mm Hg for the 15-mg, 30-mg, 60-mg, and placebo groups, respectively; $p < 0.05$ for all tolvaptan vs. placebo). Tolvaptan also reduced right atrial pressure (-4.4 ± 6.9 mm Hg [$p < 0.05$], -4.3 ± 4.0 mm Hg [$p < 0.05$], -3.5 ± 3.6 mm Hg, and -3.0 ± 3.0 mm Hg for the 15-mg,30-mg, 60-mg, and placebo groups, respectively) and pulmonary artery pressure (-5.6 ± 4.2 mm Hg, -5.5 ± 4.1 mm Hg, -5.2 ± 6.1 mm Hg, and -3.0 ± 4.7 mm Hg for the 15-mg, 30-mg, 60-mg, and placebo groups, respectively; $p < 0.05$). Tolvaptan increased urine output by 3 h in a dose-dependent manner ($p < 0.0001$), without changes in renal function.

Conclusions In patients with advanced HF, tolvaptan resulted in favorable but modest changes in filling

pressures associated with a significant increase in urine output. These data provide mechanistic support for the symptomatic improvements noted with tolvaptan in patients with decompensated HF.

Take-home message:

Hyponatremia in patients with heart failure may reflect a marker of neurohormonal activation and hence the severity of this disease. With the elaboration of AVP dysregulation in heart failure and introduction of vasopressin antagonist (such as tolvaptan) to clinical practice, a promising strategy is now at the horizon for a better management of patients with heart failure.

References:

1. De Luca L, Klein L, Udelson JE, Orlandi C, Sardella G, Fedele F, Gheorghiade M. Hyponatremia in Patients with Heart Failure The American Journal of Cardiology, Volume 96, Issue 12, Supplement 1, 19 December 2005, Pages 19-23.
2. Marco Metra, MD,^a Livio Dei Cas, MD,^a and Michael R. Bristow, MR, MD, PhD^b Brescia, Italy; and Denver, CO The pathophysiology of acute heart failure—It is a lot about fluid accumulation Am Heart J 2008;155:1-5.
3. Udelson JE, Orlandi C, Ouyang J, Krasa H, Zimmer CA, Frivold G, W. Haught WH, Meymandi S, Macarie C, Raef D, Wedge P, Konstam MA, Gheorghiade M Acute Hemodynamic Effects of Tolvaptan, a Vasopressin V2 Receptor Blocker, in Patients With Symptomatic Heart Failure and Systolic Dysfunction: An International, Multicenter, Randomized, Placebo-Controlled Trial. Journal of the American College of Cardiology, Volume 52, Issue 19, 4 November 2008, Pages 1540-1545
4. Sterns RH and Stephen M. Silver Seldin and Giebisch's The Kidney (Fourth Edition), 2008, Pages 1179-1202
5. Berl T, Schrier RW. Vasopressin Antagonists in Physiology and Disease Textbook of Nephro-Endocrinology, 2009, Pages 249-260

6. Schlanger LE and Sands JM Vasopressin in the Kidney: Historical Aspects. Textbook of Nephro-Endocrinology, 2009, Pages 203-223
7. Lee CR, Watkins ML, Patterson JH, Gattis W, O'Connor CM, Gheorghiade M, Adams KF, Jr Vasopressin: a new target for the treatment of heart failure. American Heart Journal, Volume 146, Issue 1, July 2003, Pages 9-18
8. Thierry H. LeJemtel □, Claudia Serrano Vasopressin dysregulation: Hyponatremia, fluid retention and congestive heart failure. International Journal of Cardiology 120 (2007) 1–9

HYPERNATREMIA

Iyan Darmawan

Hypernatremia (serum sodium of more than 150 mEq/L) is a common electrolyte disturbance in hospitalized patients and in patients admitted to medical and surgical intensive care units (ICUs). Hypernatremic patients were classified into 3 groups: (a) mild, maximum serum sodium of 151 to 155 mEq/L; (b) moderate, maximum serum sodium of 156 to 160 mEq/L; and (c) severe, maximum serum sodium of more than 160 mEq/L.¹ This categorization, although to some extent arbitrary, was derived from the recommendations of Bingham and the Brain Trauma Foundation.

Although some patients, such as the elderly, mentally handicapped individuals, and residents of nursing homes are admitted with hypernatremia ², in most instances, hypernatremia is a condition that develops after hospitalization. Hypernatremia is usually a result of increased free water losses (renal, enteral, and insensible) in association with decreased free water intake (impaired thirst mechanism, lack of access to free water) and inappropriate therapy with isotonic fluids. Hospitalized patients with hypernatremia have a significantly higher mortality rate (40%-60%) compared with patients without hypernatremia, and mortality is higher in patients with hospital-acquired hypernatremia when compared with patients with hypernatremia at admission. The reported frequency of hypernatremia in a general hospital population ranges from 0.3% to 3.5% .

Patients admitted to an ICU have a higher incidence of hypernatremia compared with the general. Hospital mortality was 33.5% in the hypernatraemic group and 7.7% in the normonatraemic group ($p < 0.001$).³ Because hypernatremia is frequently an iatrogenic condition associated with high mortality, some authors have suggested that it could be used as an indicator of quality of care .Critically ill patients with neurologic and

neurosurgical diseases have many factors that make them especially susceptible to developing hypernatremia. They often have impaired thirst mechanisms due to altered sensorium or disorders of the nervous systems affecting thirst perception.

These patients may also have diabetes insipidus because of pituitary or hypothalamic dysfunction. Increased insensible loss from central fever is also a contributing factor. More importantly, in patients with cerebral edema and raised intracranial pressure, hypernatremia frequently results from the therapeutic use of osmotic diuretics (mannitol) or hypertonic saline.

Hypernatremia may have a therapeutic role in patients receiving osmotic therapy. In adults with postoperative or posttraumatic cerebral edema treated with 3% saline, a reduction in intracranial pressure has been shown to correlate with rise in serum sodium level. In pediatric head-injured patients treated with hypertonic saline, hypernatremia correlates with better control of intracranial pressure without significant side effects.

Hypernatremia, however, has also been shown to be associated with an increased incidence of renal dysfunction in this population. Thus, in patients receiving osmotic therapy, the ideal sodium level is often difficult to determine. On one hand, hypernatremia may be beneficial in controlling intracranial pressure. On the other hand, based on studies done in general medical-surgical wards and ICUs, hypernatremia could be associated with increased morbidity and mortality

To appropriately treat patients with osmotic therapy, it is essential to study the impact of hypernatremia on mortality in this unique patient population. It is also important to try to identify a threshold to which the serum sodium level can be safely raised. The relationship between hypernatremia and mortality in these patients has not been studied previously.

Some considerations before treating hypernatremia ^{1,4}:

1. Hypernatremia always indicates the presence of cellular dehydration
2. In most cases, the cause is net water loss (eg after mannitol)
3. Overloading of sodium (Meylon) can also contribute
4. More frequently in infants, elderly and neurological patients. In the elderly symptoms have not appeared before sodium level exceeds 160 mmol/L
5. In acute hypernatremia (occurring within hours), the recommended rate of reduction 1 mmol/L/hour. In chronic hypernatremia, the rate of correction is 0.5 mmol/L/hour in order to avoid cerebral edema. (more correctly 10 mmol/L/24 hours)
6. Obligatory maintenance requirement needs to be added.
 - In principle 1 L of sodium containing solution will increase or decrease plasma Na^+ concentration
 - The magnitude of change of plasma Na^+ concentration can be calculated with the formula:
$$\frac{\text{Infusate Na}^+ - \text{serum Na}^+}{\text{Total body water} + 1}$$
 - Total body water in adults is 60% of body weight, whereas in children 70% of body weight

Case Illustration

A 76-year-old man presents with a severe obtundation, dry mucous membranes, decreased skin turgor, fever, tachypnea, and a blood pressure of 142/82 mmHg without orthostatic changes. The serum sodium concentration is 168 mmol per liter, and the body weight is 68 kg. Hypernatremia caused by pure water depletion due to insensible water losses is diagnosed. Infusion of KAEN 4A (Na^+ 30, Cl^- 30 mmol/L) is planned.

Planned treatment to correct Na^+ in over 24 hours to reach 158 mmol/L, hoping that sensorium improves.. What are the amount and rate of administration of KAEN 4A required?

$$\frac{\text{Infusate } \text{Na}^+ - \text{Serum } \text{Na}^+}{\text{Total body water} + 1}$$

$$\frac{30 - 168}{60\% \text{BW} + 1} =$$

$$\frac{-138}{(60\% \times 68) + 1} =$$

$$\frac{-138}{41.80} = -3.2$$

Meaning 1 L of KAEN 4A will decrease plasma Na^+ by approx. 3.2 mmol/L. The goal of treatment is to reduce the serum sodium concentration by approximately 10 mmol per liter over a period of 24 hours.

Therefore, 3 liter of KAEN 4A (10 : 3.2) is required. With 1.5 liters added to compensate for average obligatory water loss over 24 hour period, a total of 4.5 liters will be administered for the next 24 hours.

References :

1. Adrogué, HJ; and Madias, NE. Primary Care: Hyponatremia. *New England Journal of Medicine* 2000; 342(20):1493-1499
2. Chassagne P. Clinical Presentation of Hyponatremia in Elderly Patients: A Case Control Study. *J Am Geriatr Soc* 54:1225-1230, 2006
3. O'Donoghue SD Acquired hyponatremia is an independent predictor of mortality in critically ill patients *Anaesthesia*, 2009, 64, pages 514-520
4. Arief Al. , Water and Electrolyte Balance in Health and Disease. In M.S. John Pathy, Alan J. Sinclair, John E. Morley *Principles and Practice of Geriatric Medicine*, Volume 2, Fourth Edition Pages: 1367-1387, 2006

HYPOKALEMIA

Iyan Darmawan

Introduction

Hypokalemia (serum K^+ <3.5 mEq / L) is one of the electrolyte abnormalities found in hospitalized patients.

In the US, 20% of hospitalized patients experienced hypokalemia⁽¹⁾, but significant clinical hypokalemia only occurs in 4-5% of these patients. Frequency in outpatients who received diuretics is 40% ⁽²⁾. Although the levels of potassium in the serum only 2% of total body potassium and in many cases does not reflect the status of the body potassium; hypokalemia should be understood as all the medical interventions to address hypokalemia are based on serum potassium levels.

Pathophysiology

Trans-cellular movement of potassium can occur without changes in cellular potassium reserves. This is due to factors that stimulate migration from the intravascular to the intracellular potassium, among others, the load of glucose, insulin, adrenergic drugs, bicarbonate, etc. Insulin and catecholamine sympathomimetic drugs are known to stimulate the influx of potassium into muscle cells. While aldosterone stimulates Na^+/K^+ ATP-ase pump that functions as an antiport in renal tubules. This stimulation effect is sodium retention and potassium secretion.⁽¹⁾

Patients with asthma under albuterol nebulization will have decreased serum K^+ levels of 0.2 to 0.4 mmol/L^(2, 3) while the second dose given within one hour will reduce by 1 mmol/L³. Ritodrine and terbutaline, ie inhibitors of uterine contractions can decrease serum potassium to as low 2.5 mmol per liter after intravenous administration for 6 hours

Theophylline and caffeine are not sympathomimetic

drug, but they can stimulate the release of sympathomimetic amines as well as increase the activity of Na^+/K^+ ATP-ase pump. Severe hypokalemia is almost always a typical picture of acute theophylline poisoning. Caffeine in several cups of coffee could lower serum potassium by 0.4 mmol/L. Because insulin pushes potassium into cells, giving this hormone always causes a temporary reduction of serum potassium. However, this is rarely a clinical problem, except in the case of an overdose of insulin or during treatment of diabetic ketoacidosis.

Other medications that can cause hypokalemia include the following:

- Thiazide diuretics
 - Hydrochlorothiazide
 - Chlorothiazide (Diuril)
 - Indapamide (Lozol)
 - Metolzaone (Zaroxolyn)
- Loop diuretics
 - Furosemide (Lasix)
 - Bumetanide (Bumex)
 - Torsemide (Demadex)
 - Ethacrynic acid (Edecrin)
- Corticosteroids
- Amphotericin B (Fungizone)
- Antacids
- Insulin
- Fluconazole (Diflucan): Used to treat fungal infections
- Theophylline (TheoDur): Used for asthma
- laxatives
- Other potential interactions include: Digoxin - Low blood levels of potassium increase the likelihood of toxic effects from digoxin.

Potassium Depletion

Hypokalemia can also be a manifestation of the depletion of body potassium reserve. Under normal circumstances, an estimated total body potassium 50 mEq / kg body weight and plasma potassium from 3.5 to 5 mEq /L. Insufficient K^+ intake in the diet results in depletion of body potassium reserves. Although the kidney responds accordingly by reducing the excretion of K^+ , the mechanism through this regulation is only enough to prevent the occurrence of severe potassium depletion. In general, if the intake of potassium is reduced, the degree of potassium depletion is moderate. Reduced intake to <10 mEq / day resulted in a cumulative deficit of 250 sd 300 mEq (approximately 7-8% of total body potassium) in 7-10 hari⁴. After that period, losing kidney is minimal. Young adults can consume up to 85 mmol of potassium per day, while the elderly who live alone or weak may not get enough potassium in their diet ⁽²⁾.

Loss of K^+ Through Extra-renal Line

Meaningful Loss through the feces (diarrhea) and sweating may occur. Laxatives can cause excessive loss of potassium from the feces. It should be suspected in patients who want to lose weight. Some other circumstances which could lead to depletion of potassium is gastric drainage (suction), vomiting, fistula, and transfusion of erythrocytes.

Loss of K^+ Through the Kidney

Potassium-wasting diuretics and aldosterone are two factors that can deplete the body's potassium reserves. Thiazide diuretics and furosemide are two of the largest reported to cause hypokalemia.

Clinical Implications in Heart Disease Patients⁽²⁾

Not surprising that the depletion of potassium is often seen in patients with CHF. There is growing evidence to suggest that increased potassium intake can lower blood pressure and reduce stroke risk. Hypokalemia occurs in non-complicated hypertensive patients who were given diuretics, but not as often in patients with congestive heart failure, nephrotic syndrome, or cirrhosis of the liver. Protective effect of potassium on blood pressure may also reduce the risk of stroke.

Potassium depletion has been associated in the pathogenesis and persistence of essential hypertension. There is often a misinterpretation of an ACE-inhibitor therapy (eg, captopril). Because these drugs increase the retention of potassium, doctors are reluctant to add potassium or potassium-sparing diuretics on ACE-inhibitor therapy. In many cases of congestive heart failure treated with ACE-inhibitors, the drug dose is not sufficient to provide protection against loss of potassium. Potential complications of digoxin to cause cardiac arrhythmias increases if there is hypokalemia in patients with heart failure. In these patients it is recommended to maintain potassium levels in the range of 4.5 to 5 mmol / L. Nolan et al. get low serum potassium levels associated with sudden cardiac death in a clinical trial of 433 patients in the UK. Mild hypokalemia may increase the likelihood of cardiac arrhythmias in patients with cardiac ischemia, heart failure, or right ventricular hypertrophy. This implied that internist should be more aware of the various consequences of hypokalemia. Additional potassium intake should be considered if serum levels between 3.5 to 4 mmol / L. So, do not wait until levels reach <3.5 mmol / L.

The degree of hypokalaemia

Moderate hypokalemia was defined as serum levels between 2.5 to 3 mEq / L, whereas severe hypokalemia defined as serum levels <2.5 mEq / L. Hypokalemia of

<2 mEq / L is usually accompanied by heart dysfunction and life-threatening.

Hypokalemia in Children

Hypokalemia in children is also a common electrolyte disorder encountered and have diverse and serious manifestations, such as muscle paralysis, paralytic ileus, respiratory muscle paralysis, cardiac arrhythmias and even cardiac arrest. From a prospective study of 1350 hospitalized children⁶, the diagnosis of hypokalemia was considered in any child with acute and chronic diarrhea with clinical picture of drooping neck, limb weakness, and abdominal distension. A total of 38 children diagnosed as hypokalemia, the symptoms vary as follows:

As many as 85% of children with hypokalemia suffered from malnutrition and 50% of them considered severely malnourished. Various etiologies of hypokalemia include acute and chronic gastroenteritis, renal tubular acidosis, bronchopneumonia, and the use of diuretics. Giving oral potassium (20 mEq / L) in mild cases and intravenous infusion of 40 mEq / L in severe cases, known to safely and effectively cope with hypokalemia.

Hypokalemia in Surgical Patients ⁽⁷⁾

Hypokalemia is commonly found in surgical patients. Serum K^+ <2.5 mmol / L is dangerous and should be managed immediately before anesthesia and surgery. A deficit of 200-400 mmol is needed to lower the K^+ from 4 to 3 mmol / L. Likewise, a similar deficit lowers K^+ from 3 to 2 mmol / L.

The causes

- Reduced intake: normal K^+ intake is 40-120 mmol / day. This is generally reduced in surgical patients who have anorexia and unhealthy.

- Increased K^+ influx into cells: alkalosis, excess insulin, β -Agonists, stress, and hypothermia. They all led to a shift of K^+ into the cell. There will be no true depletion of K^+ if this is the only cause.
- Excessive loss from the gastrointestinal tract: vomiting, diarrhea, and drainage is a typical picture of a patient before and after abdominal surgery. Misuse of laxatives in the elderly are commonly reported and may cause hypokalemia pre-operatively.
- Excessive loss of urine: the loss of gastric secretion, diuretics, metabolic acidosis, low Mg^{++} , and mineralocorticoid excess causes loss of K^+ into the urine. Mechanism of hypokalemia in gastric fluid loss is complex. If stomach fluid loss is excessive (vomiting or via nasogastric tube), increased $NaHCO_3$ will then be transported to the kidney tubules. Na^+ is exchanged for K^+ with the consequent increase in K^+ excretion. Loss of K^+ through the kidneys in response to the vomiting is the main factor that causes hypokalemia. This is due to the little content of K^+ secretion in the stomach. Metabolic acidosis results in increased transport of H^+ into the tubule. H^+ and K^+ exchange with Na^+ , and hence K^+ excretion increases
- Excessive sweating can aggravate hypokalemia.

Risk

- Cardiac arrhythmias, particularly in patients receiving digoxin.

- prolonged paralytic ileus
- Muscle weakness
- Cramp

Diagnostic Approach

- Anamnesis usually allow the identification of causative factors.
- Blood pH is needed to interpret the low K^+ . Alkalosis is always associated with hypokalemia and causes a shift of K^+ into the cell. Acidosis causes a direct loss of K^+ in the urine.

Hypokalemia in Stroke Patients

In an observational study of 421 stroke patients⁽⁸⁾, 150 patients with myocardial infarction, and 161 outpatient patients with hypertension, the following results were obtained: Hypokalemia was found more frequently in stroke patients compared to patients with myocardial infarction, ie, 84 (20%) vs 15 (10%), $p = .008$ or patients with hypertension 84 (20%) vs 13 (8%), $p < .001$. Even, when patients who had been given diuretics were excluded from the analysis, 56 (19%) vs 12 (9%) infarct patient groups, $p = .014$ and 56 (19%) vs. 4 (5%) hypertensive group, $p = .005$, respectively. In the analysis of survival, lower potassium levels on admission was associated with increased risk of death.

Management of Hypokalemia

To be able to estimate the amount of potassium replacement we should exclude the factors other than depletion of potassium which can cause hypokalemia, such as insulin and drugs. Acid-base status affect serum potassium levels.

Amount of Potassium

Although the calculation of the amount of potassium needed to replace the loss is not complicated, there is

no standard formula to calculate the amount of potassium required by patients.. However, 40-100 mmol of K^+ supplements are usually given in moderate and severe hypokalemia.

In mild hypokalemia (potassium 3 to 3.5 mEq/L) administer oral KCl 20 mmol per day and patients are encouraged to eat foods that contain lots of potassium. Oral KCL is less tolerated by patients because it can cause gastric irritation. Foods that contain potassium is quite a lot and provide 60 mmol of potassium⁽⁵⁾

Infusion rate of Intravenous Potassium

Administration rate should not be confused with the dose. If the serum level > 2 mEq / L, then the usual rate of potassium is 10 mEq / h and a maximum of 20 mEq / hour to prevent the occurrence of hyperkalemia. In children, 0.5 to 1 mEq / kg / dose in 1 hour. The dose should not exceed the maximum adult dose.

At levels < 2 mEq / L, can be given at 40 mEq / hour through the central venous and strict monitoring in the ICU. For this quick correction, KCl should not be dissolved in a solution of dextrose because it triggers more severe hypokalemia.

Correction of Perioperative Hypokalemia

- KCL is commonly used to replace K^+ deficiency, as is also commonly accompanied by Cl^- deficiency.
- If the cause of chronic diarrhea, $KHCO_3$ or potassium citrate may be more appropriate.
- Oral therapy with a potassium salt accordingly if there is time for correction and no clinical symptoms.

Replacement of 40-60 mmol of K^+ produces an increase from 1 to 1.5 mmol / L in serum K^+ , but this is temporary because the K^+ will move back into the cell. Regular

monitoring of serum K^+ is required to ensure that the deficit has been corrected.

Intravenous Potassium

- KCl should be given iv if the patient can not eat and suffered from severe hypokalemia
- In general, do not add KCl into the infusion bottle. Use ready-made factory preparations. In severe hypokalemia correction (<2 mmol / L), you should use NaCl instead of dextrose. Provision of dextrose can cause a temporary decrease in serum K^+ of 0.2 to 1.4 mmol / L due to stimulation of insulin release by glucose.
- Infusion containing 0.3% KCl and NaCl 0.9% provides 40 mmol K^+ / L. This should be standard in K^+ replacement fluid.
- Large volumes of normal saline can cause fluid overload. If there is a cardiac arrhythmia, which required a more concentrated solution of K^+ , it is administered via a central vein with ECG monitoring. Regular monitoring is essential. Think carefully before giving > 20 mmol K^+ /hour.
- K^+ concentration > 60 mmol / L should be avoided through a peripheral vein, because it tends to cause pain and venous sclerosis.

Conclusion

Hypokalemia is a frequent electrolyte disorder encountered in clinical practice, and can affect adult and pediatric patients. Various factors need to be identified as the initial management. Giving potassium is not something to be feared by the clinician, if prerequisite of a safe administration rate for each degree of hypokalemia is known. Giving potassium should be considered in patients with heart disease, hypertension, stroke, or in circumstances likely to cause depletion of potassium.

References

1. Zwanger M. Hypokalemia. [emedicine.com/emerg/ topic 273.html](http://emedicine.com/emerg/topic/273.html) Retrieved January 2012
2. Cohn JN, Kowey PR, Whelton PK, Prisant LM. New Guidelines for potassium Replacement in Clinical Practice. *Arch Intern Med* 2000;160:2429-2436.
3. Gennari F.J. Hypokalemia: Current Concept. *The New England Journal of Medicine* 1998 Aug 13;339(7): 451-458
4. Tannen R.L. Potassium Disorders. In Kokko & Tannen. *Fluid and Electrolytes*. WB Saunders Company 3rd ed., p.123
5. Halperin ML, Goldstein MB. *Fluid Electrolyte and Acid-Base Physiology. A problem-based approach*. WB Saunders Co. 2nd ed., p 358
6. Sunil Gomber and Viresh Mahajan. Clinico-Biochemical Spectrum of Hypokalemia. *Indian Pediatrics* 1999;36:1144-1146
7. AJ Nicholls & IH Wilson. *Perioperative Medicine : managing surgical patients with medical problems*. OXFORD University Press; 2000.
8. Salah E. Gariballa, Thompson G. Robinson and Martin D. Fotherby. Hypokalemia and Potassium Excretion in Stroke Patients. *Journal of the American Geriatrics Society* 1997;45(12)

BARTTER SYNDROME (POTASSIUM WASTING)

Budhi Santoso

Background

In 1962, Frederic Bartter first observed the association of hyperplasia of the juxtaglomerular complex with hyperaldosteronism and hypokalemic alkalosis ¹. With the advent of polymerase chain reaction (PCR) and molecular genetic analysis techniques in the 1980s, it was found to be not one disease but several different abnormalities occurring in 4 transporters in 2 parts. Molecular genetic approaches to this problem have recently demonstrated that mutations in genes encoding the thiazide-sensitive Na-Cl cotransporter or the bumetanide-sensitive Na-K-2Cl cotransporter produce two distinctive clinical and physiological pictures featuring hypokalemic alkalosis. Mutations in the latter cause a phenotypic picture called Bartter's syndrome that includes marked hypercalciuria and marked intravascular volume depletion in the newborn ².

Definition

Bartter's Syndrome is an inherited defect in the renal tubules that causes low potassium levels, low chloride levels, which then causes metabolic alkalosis. Bartter Syndrome, is not a single disorder but rather a set of closely related disorders. These Bartter-like syndromes share many of the same physiologic derangements, but differ with regard to the age of onset, the presenting symptoms, the magnitude of urinary potassium (K) and prostaglandin excretion, and the extent of urinary calcium excretion. At least three clinical phenotypes have been distinguished:

- Classic Bartter Syndrome;
- The Gitelman Variant;
- The Antenatal Variant (also termed Hyperprostaglandin E Syndrome) ³.

Causes

The cause of these diseases have been unexplained for a long time. Recently however, from 1996 to 2002, several causes have identified. Bartter's syndrome can occur due to a loss of function mutation in NKCC2, ROMK, CLC-Kb and barttin, or a gain of function mutation of calcium-sensing receptor. Gitelman's syndrome can occur due to a loss of function mutation in NCC. Different causes need different treatment and have different prognosis. In fact, we cannot examine all DNA sequences in regular hospitals. So it is our goal to make a clinical diagnostic standard to appropriate treatment ⁴.

Symptoms ³ :

- Fatigue
- Polyuria (Increased urination)
- Polydipsia (Increased Thirst)
- Nocturia (Waking up at night to urinate)
- Generalized weakness
- Salt Cravings
- Dehydration
- Mental confusion
- Vomiting
- Muscle weakness
- Muscle spasms
- Tetany
- Failure to thrive
- Short stature (If untreated)

Lab and Physical findings ³ :

- Low serum potassium levels
- Low-normal magnesium levels
- Increased renin
- Increased aldosterone
- Metabolic Alkalosis
- Increased Prostaglandin E2 excretion
- Normal-high urinary calcium excretion

- Normal-high urinary Mg excretion
- Normal-low serum Mg levels (20% have decreased Mg levels)
- Normal – Low Blood Pressure
- Increased urinary potassium excretion
- Increased plasma angiotensin II
- Nephrocalcinosis
- Tetany, muscle spasms, Chvostek's sign and Trousseau's sign may be seen in hypokalemia, hypocalcemia, and hypomagnesemia patients. In the older literature rickets was also occasionally reported.
- In 1997, Madrigal described a type of this syndrome in Costa Rica in sixteen of the twenty patients with a "peculiar facies, distinguished by a triangularly shaped face, large eyes, and protruding ears".
- Another eight had sensorineural hearing loss determined by audiography.

Treatment ⁵:

- Bartter syndrome is treated by keeping the blood potassium level above 3.5 mEq/L. This is done by following a diet rich in potassium.
- Many patients also need salt and magnesium supplements, as well as medicine that blocks the kidney's ability to get rid of potassium. High doses of nonsteroidal anti-inflammatory drugs (NSAIDs) may also be used.
- Potassium chloride: Depends on degree of receptor dysfunction and hypokalemia. Serum potassium levels often run in the range of 2-3 mEq/L, which may require several hundred milliequivalents of potassium per day. Adult: 100-200 mEq PO qd in divided doses; easier to take with meals; Pediatric: 1-2 mEq/kg PO qd in divided doses; easier to take with meals ⁶.

- We report an infant with neonatal Bartter syndrome, who improved with potassium supplements⁷.

Outlook (Prognosis)⁸

The long-term outlook for patients with Bartter syndrome is not certain. Infants who have severe growth failure may grow normally with treatment. Although most patients remain well with ongoing treatment, some develop kidney failure.

References:

1. Frassetto LA, Batuman V. Bartter Syndrome. Retrieved January 15 2012, from <http://emedicine.medscape.com/article/238670-overview>
2. Proesmans WC. Bartter syndrome & its neonatal variant. *Eur J Pediatr* 1997; 156:669–79.
3. Watanabe S, Uchida S. Bartter's syndrome and Gitelman's syndrome: Pathogenesis, path physiology, and therapy. *Nihon Rinsho*. 2006 Feb;64 Suppl 2:504.
4. Tolkoff-Rubin N. Treatment of irreversible renal failure. In: Goldman L, Ausiello D, eds. *Cecil Medicine*. 23rd ed. Philadelphia, Pa: Saunders Elsevier; 2007: chap 133.
5. Sterns RH, Cox M, Feig PU, Singer I. Internal potassium balance and the control of the plasma potassium concentration. *Medicine*. 1981;60:339–354
6. P Saravana Kumar, et al. Neonatal Bartter syndrome. *Indian pediatrics*, Aug 2006. Vol. 43 Issue 8 Pg. 735-7.
7. Puricelli E, et al. Long-term follow-up of patients with Bartter syndrome type I and II. *Nephrol Dial Transplant*. Sep 2010;25(9):2976-81.

SIADH (SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE)

Budhi Santoso

BACKGROUND

Fluid homeostasis is influenced by water intake, and regulated by an intact of thirst mechanism, urinary excretion of free water mediated by appropriate secretion of arginine vasopressin (AVP) which also known as antidiuretic hormone. Conversely, the SIADH manifests as an inability to excrete a free water load, with inappropriately concentrated urine and resultant hyponatremia, hypo-osmolality, and natriuresis⁽¹⁾. SIADH is listed as a "rare disease" by the Office of Rare Diseases (ORD) of the National Institutes of Health (NIH). This means that SIADH, or a subtype of SIADH, affects less than 200,000 people in the US population⁽²⁾. Although SIADH is not unusual in adults, it is the most common cause of hypotonic normovolemic hyponatremia in children⁽³⁾. Exact incidence figures are not available and usually transient or may be chronic, it is often associated with drug use or a lesion in the central nervous system or lung⁽⁴⁾. The cardinal features of SIADH were defined by Bartter and Schwartz⁽¹⁾.

WHAT IS SIADH?

SIADH : The syndrome of inappropriate antidiuretic hormone⁽⁴⁾

Other names or spellings⁽⁵⁾ : Inappropriate ADH syndrome, Schwartz-Bartter syndrome, Syndrome of inappropriate antidiuretic hormone secretion

Definition: SIADH stands for syndrome of inappropriate anti-diuretic hormone. The abnormal production of this hormone ADH, leads to salt wasting, or hyponatremia. The result is a profound metabolic disturbance which may result in coma and death. The pathologist is often called upon to investigate a laboratory abnormality of serum hypo-osmolality, an unexpectedly high urinary

specific gravity, an absence of edema or dehydration, hyponatremia, and an elevation of plasma vasopressin. Usually there is normal adrenal, thyroid, and renal function. Occasionally the syndrome is due to head trauma or a tumor. In these cases, the pathologist may be called upon to evaluate a tissue biopsy to confirm the diagnosis ⁽³⁾

Epidemiology:

Most older hyponatremic patients in a rehabilitation setting seem to have SIADH etiology. This study confirms the presence of a group of older individuals with chronic idiopathic hyponatremia in whom the underlying mechanism may be SIADH related to aging. Hyponatremia is modest in these patients and has little clinical significance. However, they may be at increased risk of developing symptomatic hyponatremia with intercurrent illnesses ⁽⁶⁾. The SIADH occurred in about one-third of the children hospitalized for pneumonia, and was associated with a more severe disease and a poorer outcome. Perhaps fluid restriction in these cases may improve the outcome ⁽⁷⁾.

WHAT CAUSES SIADH?

SIADH tends to occur in people with heart failure or people with a diseased hypothalamus (the part of the brain that works directly with the pituitary gland to produce hormones). In other cases, a certain cancer (elsewhere in the body) may produce the antidiuretic hormone, especially certain lung cancers. Other causes may include the following:

- meningitis
- encephalitis
- brain tumors
- psychosis
- lung diseases

- head trauma
- Guillain-Barré syndrome (GBS) - a reversible condition that affects the nerves in the body. GBS can result in muscle weakness, pain, and even temporary paralysis of the facial, chest, and leg muscles. Paralysis of the chest muscles can lead to breathing problems.
- certain medications
- damage to the hypothalamus or pituitary gland during surgery

WHAT ARE THE SYMPTOMS OF SIADH?

Symptoms, in more severe cases of SIADH, may include:

- nausea
- vomiting
- irritability
- personality changes, such as combativeness, confusion, and hallucinations
- seizures
- stupor
- coma

The symptoms of SIADH may resemble other problems or medical conditions. Always consult your physician for a diagnosis.

HOW SERIOUS IS SIADH ⁽⁵⁾ ?

The Complications and sequelae of SIADH include:

- Hypouricemia
- Water overload
- Chloride levels low (plasma or serum)
- Low plasma osmolality

- Hypokalaemia
- Hypomagnesemia
- Sodium levels raised (urine)

Complications of SIADH are secondary conditions, symptoms, or other disorders that are caused by SIADH. In many cases the distinction between symptoms of SIADH and complications of SIADH is unclear or arbitrary.

Mortality/Morbidity ⁽⁹⁾

The presence of hyponatremia, its severity, and delay in initiating adequate treatment appear to be the main indicators for both morbidity and mortality.

- The mortality rate in patients with hyponatremia is 50-fold higher than in patients who do not develop hyponatremia. Moreover, the mortality rate in patients with serum sodium concentrations less than 120 mmol/L is 25%, or twice that, of patients with mild hyponatremia.
- Acute decreases in serum sodium in adults are associated with a cited mortality rate of 5-50%, depending on the severity and rate of development; in children, the mortality rate is only about 8%. Infants probably tolerate cerebral edema with fewer untoward effects because of their expandable cranium.
- Symptomatic postoperative hyponatremia can result in high morbidity and mortality rates in children of both sexes, which is due in large part to inadequate brain adaptation and lack of timely treatment.

DIAGNOSIS

In addition to a complete medical history and physical examination, to confirm diagnosis of SIADH, blood tests will need to be performed to measure sodium, potassium

chloride levels, and osmolality (concentration of solution in the blood).

Laboratory findings in diagnosis of SIADH is Hyponatremia <130 mEq/L, and $P_{Osm} <270$ mOsm/kg ⁽¹⁾.

Other findings includes :

- Urine sodium concentration >20 mEq/L (inappropriate natriuresis)
- Maintained hypervolemia
- Suppression of renin-angiotensin system
- No equal concentration of atrial natriuretic peptide
- Low blood urea nitrogen (BUN)
- Low creatinine
- Low uric acid
- Low albumin

Differential diagnosis

Cerebral salt wasting syndrome (CSWS) also presents with hyponatremia, but is treated differently ⁽⁸⁾.

MANAGEMENT FOR SIADH:

. Treatment may also include ⁽¹⁾:

- certain medications that inhibit the action of ADH (rarely used in children because of the side effects)
- Treating underlying causes when possible.
- surgical removal of a tumor that is producing ADH

The most common treatment for SIADH is fluid restriction of between 30 to 75 percent of normal fluid intake, depending on the severity of the disorder. If the condition is chronic, fluid restriction may need to be permanent.

Fluid management ⁽¹⁰⁾:

- Fluid intake should be restricted to 500 mL less than urinary output

- In patients with severe symptoms and signs (Hypertonic Saline can be infused at ≤ 0.05 mL/kgBW per minute), If Hyponatremia has been present for more than 24 – 48 h and its corrected too rapidly, Saline infusion has the potential to cause CPM (Central Pontine Myelinolysis).
- For very symptomatic patients (severe confusion, convulsions, or coma) hypertonic saline (5%) 200-300 ml IV in 3-4 h should be given.

Drugs Management:

Demeclocycline can be used in chronic situations when fluid restrictions are difficult to maintain; demeclocycline is the most potent inhibitor of AVP action. If treatment with the drug that caused SIADH must be continued, concomitant treatment with demeclocycline may reduce the tendency of hyponatraemia⁽¹¹⁾.

Tolvaptan⁽¹²⁾ is a novel, non-peptide, selective antagonist of the vasopressin V2 receptor, Its indications are "treatment of euvolemic hyponatremia (e.g. the syndrome of inappropriate secretion of antidiuretic hormone, or in the setting of hypothyroidism, adrenal insufficiency, pulmonary disorders, etc.) in hospitalized patients.

Amiodarone-induced SIADH may occur during the initial loading period, and it may be improved by reduction of the dose without discontinuation of the drug⁽¹³⁾.

References:

1. Feldman BJ, et al; Nephrogenic Syndrome of Inappropriate Antidiuresis; N Engl J Med 2005;352:1884-90
2. National Institutes of Health (NIH), USA. 1999.
3. Lim YJ, Park EK, Koh HC, Lee YH. Syndrome of inappropriate secretion of antidiuretic hormone as a leading cause of hyponatremia in children who underwent chemotherapy or stem cell transplantation. *Pediatr Blood Cancer*. May 2010;54(5):734-7

4. Anpalahan MD; Department of General Medicine, Western Hospital, Melbourne, Australia; J Am Geriatr Soc, 2001 Jun;49(6):788-92
5. Ganong CA, Kappy MS. Cerebral salt wasting in children. The need for recognition and treatment [published erratum appears in Am J Dis Child 1993 Apr;147(4):369]. *Am J Dis Child*. Feb 1993;147(2):167-9
6. Dhawan A, Narang A, Singhi S. Department of Paediatrics, Postgraduate Institute of Medical Education & Research, Chandigarh, India. *Ann Oncol* 2000 Aug;11(8):1061-5
7. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. *Am J Med*. Jul 2006;119(7 Suppl 1):S30-5.
8. Hoorn EJ, van der Lubbe N, Zietse R. SIADH and hyponatraemia: why does it matter?. *NDT Plus*. Nov 2009;2:iii5-iii11.
9. Braunwald, Eugene, et al. Overview: Harrison's Manual of Medicine 15th edition. Mc Graw Hill International, Boston, USA 2002. p.772
10. Hyponatraemia and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) induced by psychotropic drugs. Spigset O, Hedenmalm K. Division of Clinical Pharmacology, Norrland University Hospital, Umea, Sweden. *Drug Saf* 1995 Mar;12(3):209-25
11. Schrier Robert W. MD, Gross, Gheorghiade M, et al. "Tolvaptan, a Selective Oral Vasopressin V2-Receptor Antagonist, for Hyponatraemia". *N Engl J Med*. 2006; 355;20:29-42.
12. Ikegami H, Shiga T, Tsushima T, Nirei T, Kasanuki H. Department of Cardiology, The Heart Institute of Japan, Tokyo Women's Medical University, Shinjuku, Tokyo, Japan. *J Cardiovasc Pharmacol Ther* 2002 Jan;7(1):25-8
Abstract quote

DIABETES INSIPIDUS

Budhi Santoso

Introduction

Diabetes Insipidus is a disorder in which there is an abnormal increase in urine output, fluid intake and often thirst. It causes symptoms such as urinary frequency, nocturia (frequent awakening at night to urinate) or enuresis (involuntary urination during sleep or "bedwetting"). Urine output is increased because it is not concentrated normally. Consequently, instead of being a yellow color, the urine is pale, colorless or watery in appearance and the measured concentration (osmolality or specific gravity) is low. *Diabetes Insipidus is not the same as diabetes mellitus ("sugar" diabetes).

Diabetes Insipidus resembles diabetes mellitus because the symptoms of both diseases are increased urination and thirst. However, in every other respect, including the causes and treatment of the disorders, the diseases are completely unrelated. Sometimes diabetes insipidus is referred to as "water" diabetes to distinguish it from the more common diabetes mellitus or "sugar" diabetes (1).

Normal Fluid Regulation in the Body

The body has a complex system for balancing the volume and composition of body fluids. The kidneys remove extra body fluids from The bloodstream. This fluid waste is stored in the bladder as urine. If The fluid regulation system is working properly, The kidneys make less urine to conserve fluid when the body is losing water. The kidneys also make less urine at night when the body's metabolic processes are slower. The hypothalamus makes antidiuretic hormone (ADH), which directs the kidneys to make less urine. In order to keep the volume and composition of body fluids balanced, the rate of fluid intake is governed by thirst,

and the rate of excretion is governed by the production of antidiuretic hormone (ADH), also called vasopressin.

This hormone is made in the hypothalamus, a small gland located in the base of the brain. ADH is stored in the nearby pituitary gland and released from it into the bloodstream when necessary. When ADH reaches the kidneys, it directs the kidneys to concentrate the urine by returning excess water to the bloodstream and therefore make less urine. Diabetes insipidus occurs when this precise system for regulating the kidneys' handling of fluids is disrupted. The most common form of clinically serious diabetes insipidus, central diabetes insipidus, results from damage to the pituitary gland, which disrupts the normal storage and release of ADH.). A specialist should determine which form of diabetes insipidus is present before starting any treatment ⁽²⁾.

Four fundamentally different types of Diabetes Insipidus

1. **Neurogenic**, also known as *central*, *hypothalamic*, *pituitary* or *neurohypophyseal* is caused by a deficiency of the antidiuretic hormone, vasopressin
2. **Nephrogenic**, also known as *vasopressin-resistant* is caused by insensitivity of the kidneys to the effect of the antidiuretic hormone, vasopressin
3. **Gestagenic**, also known as *gestational* is also caused by a deficiency of the antidiuretic hormone, vasopressin, that occurs only during pregnancy.
4. **Dipsogenic**, a form of *primary polydipsia* is caused by abnormal thirst and the excessive intake of water or other liquids.

Each has a different cause and must be treated in a different way ⁽³⁾

Guidelines for Diagnosis

Urinary frequency, nocturia, enuresis, and frequent or constant thirst should arouse suspicion of DI.

Caution: Nephrogenic DI commonly occurs at birth, when thirst and polyuria will be signaled as unexplained fussiness or inconsolable crying, unusually wet diapers, frequent nursing often accompanied by fever, dry skin with cool extremities, and failure to thrive. These signs and symptoms should arouse suspicion of polyuria/polydipsia in any infant or young child who cannot yet verbalize her/his complaints. On the basis of a good history and appropriate tests, rule out diabetes mellitus, the most common cause of polyuria/polydipsia.

Usually, absence of glucose in the urine, as determined by Dipstick, will suffice. If possible, collect 24-hour urine into clean, 1 gallon, plastic milk containers during ad libitum fluid and food intake. A total volume of more than 2800 ml (40 ml/kg body weight per day or higher in adults and older children) with an osmolality below 300 mOsm/kg H₂O (specific gravity <1.010) warrants further evaluation for DI. In infants or young children who are not yet toilet trained, it may be easier to measure fluid intake; an intake of approximately 1 1/2 to 2 quarts per day (100 ml/kg body weight per day or more) will be strongly suggestive of DI. An effort should then be made to differentiate among the forms of DI, as follows

Measure plasma sodium concentration during ad libitum fluid and food intake. If plasma sodium is above normal while urine osmolality is below 300 mOsm/kg H₂O:

Measure the urine osmolality of a spontaneously voided urine sample. Immediately thereafter, give an injection of desamino, d-arginine vasopressin (dDAVP) -- 1 to 3 micrograms subcutaneously (depending on age and body weight) and measure urine osmolality 1 to 2 hours later (or of the next spontaneously voided sample).

- If the urine osmolality rises by 50% or more (e.g., from 280 mOsm/kg H₂O before dDAVP to 420 mOsm/kg H₂O or higher after dDAVP), then a diagnosis of neurogenic DI (pituitary or central DI) is likely.
- If the urine osmolality rises by less than 50%, then *nephrogenic* DI may be present.
- If plasma sodium is normal while urine osmolality is below 300 mOsm/kg H₂O, additional procedures, including a water deprivation test (sometimes with hypertonic saline infusion), will be needed for differential diagnosis.

Treatment

Central DI and gestational DI respond to desmopressin. Carbamazepine, an anti-convulsive medication, has also had some success in this type of DI. Also gestational DI tends to abate on its own 4 to 6 weeks following labour, though some women may develop it again in subsequent pregnancies. In dipsogenic DI, desmopressin is not usually an option.

Desmopressin will be ineffective in nephrogenic DI. Instead, the diuretic hydrochlorothiazide (HCT or HCTZ) or indomethacin can improve nephrogenic diabetes insipidus; HCT is sometimes combined with amiloride to prevent hypokalemia. Again, adequate hydration is important for patients with DI, as they may become dehydrated easily ⁽⁵⁾.

References:

1. Rose BD, Post TW. Clinical Physiology of Acid-Base & electrolyte disorders. McGraw-Hill 5th ed, 2001, pp 75-759
2. Wolfsdorf JI, Sperling MA. Diabetes Insipidus. In Abdelaziz Y. Elzouki (ed.), Textbook of Clinical Pediatrics, pp 3759-3762 Springer-Verlag Berlin Heidelberg 2012
3. Repaske DR. Disorders of water balance. In Brook's Clinical

Pediatric Endocrinology, Sixth Edition © 2009 Blackwell Publishing Limited. Pp 343-373

4. Andreoli TE et al. Endocrine control of water balance. In Comprehensive Physiology. © 2010 American Physiological Society. pp 539-560
5. Goldman L, Ausiello D. Goldman: Cecil Medicine. 23rd ed. Philadelphia, PA: Saunders Elsevier;2007:chap 241, 242.

HYPOGLYCEMIA IN CHILDREN & NEONATES

Iyan Darmawan

Introduction

Severe glucose deficiency leads to cerebral energy failure, impaired cardiac performance, muscle weakness and diminished glucose production ⁽¹⁾. Between 1925 and 1960, the only responses to a low plasma or blood glucose concentration that were recognized in the neonate were clinical manifestations including tremor, sweating, lethargy, floppiness, coma, and seizures. The level of glucose at which clinical manifestations occurred determined a working definition for significant hypoglycemia. Because similar manifestations can occur with a variety of other neonatal problems, for example, perinatal asphyxia, sepsis, or other metabolic abnormalities, the sine qua non for the diagnosis of significant neonatal hypoglycemia must be to satisfy Whipple's triad. In 1938, Whipple described the triad of criteria necessary for the diagnosis of hypoglycemia, i.e. symptoms consistent with hypoglycemia, blood glucose concentration less than 2.8 mmol/L and immediate relief by the ingestion of glucose ⁽²⁾

DEFINING HYPOGLYCEMIA

The definition of hypoglycemia remains controversial although most clinicians would agree that a serum glucose level of 40 to 50 mg/dL warrants further investigation ⁽³⁾

More recently, other authors in "definitive" textbooks have provided different but variable definitions of hypoglycemia:

< 2mmol/L blood(< 36mg/dL), Kalhan & Parimi ⁽⁴⁾

< 2.2mmol/L blood(< 40mg/dL), Ogata ⁽⁵⁾ and

<2.0–3.3mmol/L (< 36–40mg/dL) blood, < 2.2–2.5mmol/L(<40–45mg/dL) plasma, McGowan and Hay)⁽⁶⁾.

In standard pediatric reference texts, the normal serum glucose concentration for children beyond the newborn period is greater than or equal to 60 mg/dL (3.3mmol/L)⁽⁷⁾

A survey in the United Kingdom found that medical practitioners varied considerably in their definition of “hypoglycemia” with only limited correlation to published definitions⁽⁸⁾

In response to such variable definitions, Cornblath et al. Developed the concept of an “operational threshold,” defined as “that concentration of plasma or whole blood glucose at which clinicians should consider intervention, based on the evidence currently available in the literature (see table)⁽⁹⁾

Reference Values

	Age	Reference
The lower limit of the fasting plasma glucose concentration is normally approximately 70 mg/dL (3.9 mmol/L)* , but substantially lower venous glucose levels occur normally, late after a meal. Glucose levels <55 mg/dL (3.0 mmol/L) with symptoms that are relieved promptly after the glucose level is raised document hypoglycemia	Adults	Harrison’s Principles of <i>Internal Medicine</i> , 17e ⁽¹⁰⁾
Hypoglycemia was defined by studies as early as 1937 as “mild”, < 2.2–3.3mmol/L (40–60mg/dL) “moderate”, <1.1–2.2mmol/L (20 40mg/dL)	Pediatrics	HartmanAF, JaudonJ C. Hypoglycemia. J Pediatr 1937;11:1–36. ⁽¹¹⁾

"extreme", <1.1mmol/L(b20mg/dL)		
At very low glucose concentrations (< 20–25 mg/dL, 1.1–1.4 mmol/L), intravenous glucose infusion aimed at raising the plasma glucose levels above 45 mg/dL (2.5 mmol/L) is indicated. It should be underscored that the therapeutic objective (plasma glucose >45 mg/dL, 2.5 mmol/L) is quite different from the operational threshold for intervention (36 mg/dL, 2.0 mmol/L).	Neonates	Cornblath M, Hawdon JM, Williams AF, et al. Controversies regarding definition of neonatal hypoglycemia: suggested operational thresholds. <i>Pediatrics</i> 2000;105:1141–5. ⁽⁹⁾
Normal : ≥ 60 mg/dL (3.3mmol/L)	Beyond newborn period	Nicholson JF, Pesce MA. Reference ranges for laboratory tests and procedures. In: Behrman RE, Kleigman RM, Jenson HB, eds. <i>Nelson textbook of pediatrics</i> , 17th edn. Philadelphia: Saunders;2004:2396–427 ⁽⁷⁾

*Note: 1 mmol/L = 18 mg/dl

Clinical Signs

TABLE 1. Clinical Signs Associated With Hypoglycemia*
(3)

Acute hypoglycemia and the Autonomic Response	Prolonged Hypoglycemia and Neuroglycopenia
Sweating Weakness Hunger Shakiness, tremor	Lethargy Irritability Confusion Slurred speech

Tachycardia Nausea,vomiting	Headache Seizures
--------------------------------	----------------------

* Clinical signs should be alleviated with concomitant correction of plasma glucose levels.

Which newborns are prone to suffer from hypoglycemia? ¹⁾

Below is the table showing conditions with increased risk of neonatal hypoglycemia

Maternal conditions

1. Presence of diabetes or abnormal result to glucose tolerance test
2. Preeclampsia and pregnancy-induced or essential hypertension
3. Maternal beta blocker medication
4. Previous macrosomic infants
5. Substance abuse
6. Treatment with beta-agonist tocolytics
1. Treatment with oral hypoglycemic agents
2. Late antepartum to intrapartum administration of IV glucose

Neonatal conditions

1. Preterm birth
2. Intrauterine growth restriction
3. Perinatal hypoxia–ischaemia
4. Bacterial infection
5. Hypothermia
6. Polycythaemia–hyperviscosity
7. Rhesus haemolytic disease
8. Iatrogenic administration of insulin
9. Congenital cardiac malformations
10. Persistent hyperinsulinemia
11. Endocrine disorders
12. Inborn errors of metabolism
13. Poor feeding, especially after feeding well

Rationale of treating hypoglycemia

Severe glucose deficiency leads to cerebral energy failure, impaired cardiac performance, muscle weakness, glycogen depletion, and diminished glucose production. Also, repeated low glucose concentrations $<2.6\text{mmol/L}$ ($< 47\text{mg/dL}$), in preterm infants were associated with delayed neurological development at 18 months of age. In infant with abnormal clinical signs, If the value is $<45\text{ mg/dL}$ (2.5 mmol/L), clinical interventions aimed at increasing the blood glucose concentration are indicated ⁽⁹⁾

Preterm Infants

There are no recent data to support the adoption of lower operational thresholds for the preterm infant. Previous observational data suggesting lower plasma glucose in the preterm reflected the prevailing nutritional management of these small infants. One retrospective study of preterm infants has suggested a cutoff value of 47 mg/dL (2.6 mmol/L) ⁽¹²⁾

Treatment*

Plasma glucose levels less than 50mg/dL and patients with symptomatic hypoglycemia should be treated with intravenous dextrose 0.2g/kg bolus or 2mL/kg of 10% dextrose solution. A continuous 10% dextrose infusion should be continued at a rate of 5mL/kg per hour (approximates 8mg/kg per minute), and the blood glucose level should be checked every 30 to 60 minutes until stabilization occurs. The dextrose bolus may be repeated if hypoglycemia recurs, and the glucose infusion rate may be increased up to 10mL/kg per hour ⁽³⁾

HYPOGLYCEMIA COMPLICATING DEHYDRATION IN CHILDREN WITH ACUTE GASTROENTERITIS ⁽¹³⁾

A study was done to estimate the prevalence of hypoglycemia among children with dehydration due to acute gastroenteritis, and to identify clinical variables associated with hypoglycemia in these children. A retrospective case series of children older than 1 month of age and younger than 5 years of age who presented to an urban children's hospital Emergency Department with acute gastroenteritis and dehydration was performed. Medical records were reviewed; demographic and clinical data, including pretreatment serum glucose concentrations, were recorded. There were 196 children comprising the study population. Eighteen children (9.2%) were hypoglycemic.

The duration of vomiting was longer for the children with hypoglycemia (2.6 days, $SD \pm 1.5$) than for those without hypoglycemia (1.6, $SD \pm 1.8$), 95% CI 0.13 to 1.88. Hypoglycemia may complicate dehydration due to acute gastroenteritis in young children. Clinicians should examine the serum glucose concentration in these children.

Glucose-containing solutions, such as Asering-5 (acetated ringer's in 5% dextrose) and KAEN3B should be considered when vomiting is severe in acute gastroenteritis.

Foot notes:

Asering-5 : acetated ringer's in 5% dextrose (Na^+ 130 mmol, Ca^{++} mmol, K^+ 4 mmol, Cl^- 109 mmol, acetate 28 mmol, glucose 50 g per L); KAEN3 B is a maintenance solution containing Na^+ 50 mmol, K^+ 20 mmol, Cl^- 50 mmol, lactate 20 mmol, glucose 27 g per L)

II How to make 10% glucose pediatric maintenance solution from KAEN4A by adding 40% glucose

KAEN 4A is a maintenance solution containing 30 mEq Na^+ , 30 mEq Cl^- , and 4% glucose.

1. For example daily fluid requirement ~ 500 ml and 50 g glucose

40% glucose means 400 g glucose/L or 0.40 g/ml

2. KAEN 4A 500 ml contains 20 g glucose. Additional glucose required from ampoule of 40% glucose is 30 g. Therefore volume of 40% glucose required = $30 : 0.40 = 75$ ml (3 ampoules)

$$\text{Final osmolarity} = \frac{500 \times 284 + 75 \times 2222}{500 + 75} = 413 \text{ mOsm/L}$$

3. Amount of 40% glucose needed is 75 ml (3 ampoules) premixed into 500 ml of KAEN 4A

Infant has defense mechanism to utilize energy source other than glucose, i.e. Lactate (also metabolized by infant's brain). Thus the critical role of giving enough glucose is to minimize the consequences of hypoglycemia.

CONCLUSION

Blood glucose level is one of the most frequent laboratory tests performed in children and neonates, given the bad consequences of hypoglycemia. However, definition of hypoglycemia varies widely and can create confusions to clinicians. Prompt diagnostic and treatment is a challenge for emergency physicians and pediatricians.

REFERENCES:

1. Rozance PJ, Hay WW Jr. Describing hypoglycemia — Definition or operational threshold? Early Human Development, Volume 86, Issue 5, May 2010, Pages 275-280
2. Boynee MS Hypoglycemia/Hypoglycaemia Encyclopedia of Food Sciences and Nutrition, 2003, Pages 3204-3211)
3. Josefson J & Zimmerman D. Hypoglycemia in the emergency department. Clinical Pediatric Emergency Medicine VOL. 10, NO. 4, DECEMBER 2009, PP285-291)

4. Kalhan SC, Parimi PS. Metabolic and endocrine disorders, part one: disorders of carbohydrate metabolism. In: Martin RJ, Fanaroff AA, Walsh MC, editors. Neonatal-perinatal medicine: diseases of the fetus and newborn. 8th ed. Mosby-Elsevier: Philadelphia; 2006. p. 1467–91
5. Ogata ES. Carbohydrate homeostasis. In: MacDonald MG, Seshia MMK, Mullett MD, editors. Avery's Neonatology. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 876–91
6. McGowan JE, Price-Douglas W, Hay Jr WW. Glucose homeostasis. In: Merenstein G, Gardner S, editors. Handbook of Neonatal Intensive Care. 6th ed. St. Louis.: Mosby-Elsevier; 2006. p. 368–90
7. Nicholson JF, Pesce MA. Reference ranges for laboratory tests and procedures. In: Behrman RE, Kleigman RM, Jenson HB, eds. Nelson textbook of pediatrics, 17th edn. Philadelphia: Saunders; 2004: 2396–427
8. Koh TH, Eyre JA, Aynsley-Green A. Neonatal hypoglycaemia : the controversy regarding definition. Arch Dis Child 1988; 63: 1386–8.
9. Cornblath M, Hawdon JM, Williams AF, et al. Controversies regarding definition of neonatal hypoglycemia: suggested operational thresholds. Pediatrics 2000; 105: 1141–5.
10. Harrison's Principles of Internal Medicine, 17e
11. Hartman AF, Jaudon JC. Hypoglycemia. JPediatr 1937; 11: 1–36.
12. Lucas A, Morley R, Cole JJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia. Br Med J. 1988; 297: 1304–1308
13. Samuel R. Reid, Joseph D. Losek. Hypoglycemia complicating dehydration in children with acute gastroenteritis Journal of Emergency Medicine, Volume 29, Issue 2, August 2005, Pages 141-145

UPDATE ON OSMOTHERAPY

Iyan Darmawan

Introduction

Cerebral edema is frequently encountered in clinical practice in critically ill patients with acute brain injury from diverse origins and is a major cause of increased morbidity and death in this subset of patients. The consequences of cerebral edema can be lethal and include cerebral ischemia from compromised regional or global cerebral blood flow (CBF) and intracranial compartmental shifts due to intracranial pressure gradients that result in compression of vital brain structures. The overall goal of medical management of cerebral edema is to maintain regional and global CBF to meet the metabolic requirements of the brain and prevent secondary neuronal injury from cerebral ischemia. Medical management of cerebral edema involves using a systematic and algorithmic approach, from general measures (optimal head and neck positioning for facilitating intracranial venous outflow, avoidance of dehydration and systemic hypotension, and maintenance of normothermia) to specific therapeutic interventions (controlled hyperventilation, administration of corticosteroids and diuretics, osmotherapy, and pharmacological cerebral metabolic suppression).

Cerebral blood flow (CBF): basic concepts ⁽¹⁾

Prevention of secondary brain injury

When managing critical brain injuries, the aim is to prevent, recognize and treat conditions known to cause secondary brain injury. These include injuries from developing or maturing intracerebral contusions, haematomas and oedema. Such secondary injuries cause increased intracranial pressure (ICP) associated with a reduction in CBF. The reduction in CBF

compounds the insult and acts as a final common pathway for brain injury.

Cerebral ischaemia results when there is inadequate cerebral blood flow to meet the cerebral metabolic rate of oxygen consumption. Maintaining adequate CBF and reducing the cerebral metabolic rate by sedating patients and preventing hyperthermia can reduce the risk of cerebral ischaemia. The reduction of an elevated ICP also improves CBF.

CBF is proportional to cerebral perfusion pressure (CPP) and inversely related to cerebral vascular resistance (CVR):

$$CBF = CPP / CVR$$

CBF and CVR are difficult to obtain in clinical practice. CPP can be readily calculated if the mean arterial pressure (MAP) and ICP are measured, providing a surrogate assessment of CBF:

$$CPP = MAP - ICP$$

The derivation of CPP is of paramount importance in the treatment of raised ICP. Raised ICP and low CPP are associated with increased mortality after TBI. There is a clear increase in mortality when average ICP is >20 mmHg.¹

Normal values

The brain comprises 2% of body weight but it receives 17% of the cardiac output and utilises 20% of the body's oxygen.

The CBF at rest is approximately:

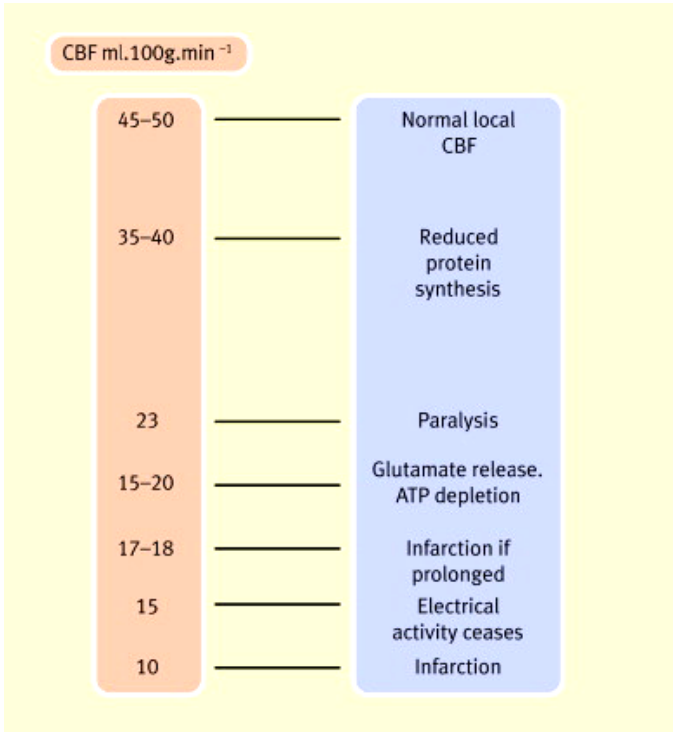
- 50 ml/100 g/minute in the grey matter

- 20 ml/100 g/minute in the white matter.

There is close coupling between CBF and local metabolic demands, leading to considerable local variation at a given time.

Cellular functions

Experiments have enabled thresholds for failure of cellular functions to be defined (Figure 1). These are most notable in the grey matter, where a higher metabolic rate exists. Thesholds for reduced protein synthesis, neurological deficits, loss of electrical activity and cell death have been defined (Figure 1).



Cerebral edema, simply defined as an increase in brain water content (above the normal brain water content of approximately 80%) and invariably a response to a

primary brain insult, is commonly observed in a variety of brain injury paradigms, including TBI, SAH, ischemic stroke and ICH, primary and metastatic neoplasms, inflammatory diseases (meningitis, ventriculitis, cerebral abscess, and encephalitis), and severe toxic– metabolic derangements (hyponatremia and fulminant hepatic encephalopathy). In the clinical setting, cerebral edema is a frequent cause of morbidity and death in patients with neural injuries.

Cerebral edema has traditionally been classified into three major subtypes: cytotoxic, vasogenic, and interstitial (hydrocephalic). This classification is highly simplistic, given that it pertains to complex pathophysiological and molecular mechanisms, but is valuable as a simple therapeutic guide for treatment of cerebral edema. Most brain insults involve a combination of these fundamental subtypes of edema, although one can predominate depending on the type and duration of injury. Cytotoxic edema results from swelling of the cellular elements (neurons, glia, and endothelial cells) because of substrate and energy failure, and affects both gray and white matter. This edema subtype is conventionally thought to be resistant to any known medical treatment. Vasogenic edema that results from breakdown of the BBB due to increased vascular permeability, as commonly encountered in TBI, neoplasms, and inflammatory conditions, predominantly affects white matter. This edema subtype is responsive to both steroid administration and osmotherapy. Other causes of vasogenic edema include tissue hypoxia and water intoxication that maybe responsive to osmotherapy but resistant to steroid administration. Interstitial edema, a consequence of impaired absorption of CSF, leads to increases in transependymal CSF flow, resulting in acute hydrocephalus. This edema subtype is also not responsive to steroid administration, and its response to osmotherapy is debatable.

The normal ICP is 5 - 15 mmHg. Most cases of brain injury that result in elevated ICP begin as focal cerebral edema. The consequences of focal (with or without ICP elevation) or global cerebral edema can be lethal and include cerebral ischemia from compromised regional or global CBF and intracranial compartmental shifts due to ICP gradients, resulting in compression of vital brain structures (herniation' syndromes). Prompt recognition of these clinical syndromes and institution of targeted therapies constitutes the basis of cerebral resuscitation. It is imperative to emphasize the importance of a patient displaying cerebral herniation syndrome without increments in global ICP; in these cases, elevations in ICP may or may not accompany cerebral edema, particularly when the edema is focal in distribution.

Pathophysiologic basis for osmotherapy ⁽²⁾

It is suggested that like most osmotic agents, mannitol and HS generally exert similar mechanisms of action in the brain; an early effect (15 to 20 min) on ICP due to optimization of rheological properties of the blood resulting in decreased blood viscosity and hematocrit (volume, rigidity and cohesiveness of red blood cell membranes), increasing CBF and oxygen delivery, resulting in reflex autoregulatory vasoconstriction of cerebral arterioles that reduces CBV and ICP ; this is followed by osmotic shrinkage of brain cells which reaches peak effect at 15 to 30 min after administration and may last from 90 min to 6 h depending on the specific etiology resulting in reduced brain water content and ICP. The rheologic effects are most effective with rapid bolus administration rather than continuous infusion. Other properties of mannitol include reduction in systemic vascular resistance (and hence afterload), combined with transiently increased preload and a mild positive inotropic effect resulting in improved cardiac output and oxygen delivery, and scavenging of toxic oxygen free radicals with potential cytoprotection. However, intravascular volume is often reduced

following its diuretic effect and fluid replacement is an important component of mannitol therapy to avoid both hypovolemia resulting in secondary ischemic injury or elevation of ICP due to reflex vasodilation of cerebral arterioles].

HS solutions which are available and used in concentrations ranging from 2% to 23.4% produce increasing osmotic gradients with higher concentrations although there is little clinical evidence for choosing one concentration over another in terms of attenuating brain water content . HS solutions have a different mechanism of action of diuresis compared to mannitol which is freely filtered at the glomerulus and decreases the reabsorption of water (and to a lesser extent sodium) accounting for its diuretic effect and hyponatremia. It is postulated that HS produces its diuretic effect from stimulation of atrial natriuretic peptide (ANP) release rather than direct osmotic diuresis which accounts for its ability to augment intravascular volume and cardiac performance, avoiding hypotension and hypovolemia . Improved CBF and oxygen delivery are believed to occur via dehydration of cerebrovascular endothelial cells, increasing vessel diameter and improving deformability of red blood cells. HS may also produce more complex therapeutic actions including reducing the inflammatory response and immunomodulatory effects via decreasing endothelial cell edema, reducing leukocyte adherence and migration which may further attenuate secondary brain injury. In TBI, HS may improve cellular function by re-establishing electrochemical gradients, restoring normal resting membrane potential and may interrupt cell hyperstimulation and subsequent cell

Osmotherapy with mannitol*

The conventional osmotic agent mannitol, when administered at a dose of 0.25 to 1.5 g/kg by intravenous bolus injection, usually lowers ICP, with maximal effects observed 20 to 40 minutes following its administration.

Repeated dosing of mannitol may be instituted every 6 hours and should be guided by serum osmolality to a recommended target value of approximately 320 mOsm/L; higher values result in renal tubular damage. This therapeutic goal is based on limited evidence, however, and higher values can be targeted provided that the patient is not volume depleted.

Osmotherapy with hypertonic saline solutions#

A variety of formulations of hypertonic saline solutions (eg 3 and 7.5 %) are used in clinical practice for the treatment of cerebral edema with or without elevations in ICP. Potassium supplementation (20–40 meq/L) is added to the solution as needed. Continuous intravenous infusions are begun through a central venous catheter at a variable rate to achieve euvolemia or slight hypervolemia (1–2 ml/ kg/hr). A 250-ml bolus of hypertonic saline can be administered cautiously in select patients if more aggressive and rapid resuscitation is warranted. Normovolemic fluid status is maintained, guided by central venous pressure or pulmonary artery wedge pressure (if available). The goal in using hypertonic saline is to increase serum sodium concentration to a range of 145 to 155 mEq/L (serum osmolality approximately 300–320 mOsm/L), but higher levels can be targeted cautiously. This level of serum sodium is maintained for 48 to 72 hours until patients demonstrate clinical improvement or there is a lack of response despite achieving the serum sodium target.

During withdrawal of therapy, special caution is emphasized due to the possibility of rebound hyponatremia leading to exacerbation of cerebral edema. Serum sodium and potassium are monitored every 4 to 6 hours, during both institution and withdrawal of therapy, and other serum electrolytes are monitored daily (particularly calcium and magnesium). Chest radiographs are obtained at least once every day to try and find evidence of pulmonary edema from congestive

heart failure, especially in elderly patients with poor cardiovascular reserve.

Efficacy and safety of hypertonic saline solutions in the treatment of severe head injury ⁽³⁾

A study was undertaken to evaluate the efficacy and safety of hypertonic saline (HS) in the treatment of intracranial hypertension after severe head injury.

Methods

This prospective, observational study was performed in an neurosurgery intensive care unit of a teaching hospital. From February 2002 to September 2004, 18 severely head-injured patients with elevated intracranial pressure (ICP) and Glasgow Coma Scale scores of 5 to 8 (mean, 5.9 ± 1.2) were admitted to the unit and treated according to a standard protocol. One dose per day of 3% saline was administered by rapid infusion (300 mL/20 min) when ICP values exceeded 20 mm Hg. After infusion, cerebral blood flow, ICP, blood pressure, end-tidal carbon dioxide, and heart rate were monitored continuously for 60 minutes and recorded. Serum osmolality, sodium, potassium, chloride, arterial carbon dioxide pressure, arterial oxygen pressure, hemoglobin, lactic acid, and pH were measured immediately before infusion (zero time) and 20 and 60 minutes after infusion. Mean arterial pressure, cerebral perfusion pressure (CPP), mean flow velocity (MFV), and pulsatility index (PI) were also recorded and analyzed.

Results

Intracranial pressure fell immediately after initiation of infusion with further significant decreases observed at 20 and 60 minutes (30.4 ± 8.5 , 24.3 ± 7.4 , and 23.8 ± 8.3 mm Hg, respectively; $P < .01$). At these respective times CPP increased significantly (78.7 ± 8.7 , 83.2 ± 7.8 , and 87.2 ± 12.8 mm Hg), PI dropped rapidly (1.51 ± 0.42 , 1.38 ± 0.32 , and 1.34 ± 0.33) and MFV increased (66.26 ± 25.91 , 71.92 ± 28.13 , and 68.74 ± 28.44). Serum

sodium increased from 141.3 ± 7.2 to 146.3 ± 7.2 mmol/L after 20 minutes and returned to 144.3 ± 7.36 mmol/L at 60 minutes. Potassium concentrations decreased significantly from 3.9 ± 0.39 to 3.55 ± 0.35 mmol/L after 20 minutes ($P < .01$). Lactic acid values at 0, 20, and 60 minutes were 1.6 ± 0.5 , 1.47 ± 0.48 , and 1.38 ± 0.53 mmol/L, respectively ($P < .01$).

Conclusion

Rapid infusion of single dose daily of HS is a safe alternative for the treatment of elevated ICP in severe head injury. Further evaluations of long-term consequences and complications and of maximal tolerance to this treatment are required.

Footnote: * Mannitol is marketed in Indonesia as OTSU-MANITOL®

3% NaCl available as OTSU-NS 3% ®

References:

1. Gilkes GE, Whitfield PC Intracranial pressure and cerebral blood flow *Surgery (Oxford)*, Volume 25, Issue 12, December 2007, Pages 530-535
2. Wendy C. Ziai, Thomas J.K. Toung, Anish Bhardwaj Hypertonic saline: First-line therapy for cerebral edema? *Journal of the Neurological Sciences*, Volume 261, Issues 1-2, 15 October 2007, Pages 157-166
3. Sheng-Jean Huang, Lin Chang, Yin-Yi Han, Yuan-Chi Lee, Yong-Kwang Tu Efficacy and safety of hypertonic saline solutions in the treatment of severe head injury *Surgical Neurology*, Volume 65, Issue 6, June 2006, Pages 539-546

NEW PARADIGM IN MAINTENANCE FLUID THERAPY

Iyan Darmawan

Abstract:

Maintenance fluid therapy can be viewed as an important supportive therapy for hospitalized patients. Unlike resuscitation fluid therapy where the goal is to restore hemodynamic derangement, maintenance therapy is aimed at maintaining homeostasis in patients who have insufficient oral intake of fluid. Accordingly, the rate of administration and type of infusion solution differ. Replacement solutions, such as normal saline, ringer's acetate/lactate are used primarily for acute replacement of emergency fluid loss, although in certain clinical situation they can be given, based on the electrolyte profile of individual patients. In the past, maintenance solution was typically represented by combination of 0.45% saline and 5% dextrose with addition of 20 mmol of K^+ . Several ready-for-use maintenance solutions have long existed, such as KAEN solutions and Half-Strength Darrow. Then, the rationale of maintenance fluid therapy was to provide sufficient potassium for homeostasis or minimum requirement and prevention of nosocomial infection from inadvertent admixture of potassium chloride into infusion solutions. It was also considered that the content of sodium in replacement solutions exceeds daily requirement. This view needs to be verified nowadays when cases of hyponatremia have frequently been reported, especially in patients with overt stimulation of AVP (arginine –vasopressin) release⁽¹⁾. Clinicians should realize that no one product can be used for every patients. "One size does not fit all".

Recently, dual chamber technology has been developed by top notch pharmaceutical companies which enables the advanced formulation containing other essential microminerals, trace elements and simultaneous administration of glucose and amino acids in single

containers. This has paved a way for the introduction of novel maintenance solution with practical and complete features for better clinical outcome.

Introduction

There have been long persistent common perceptions among clinicians, such as:

1. Fluid therapy is taken for granted. It never gets compliment when patients are successfully treated, but becomes the culprit when patient's condition worsens.
2. RL & Normal saline are also maintenance solutions administered at very low rate. This leads to generalization that they can be used for every cases.
3. Giving 2 L 5% Dextrose daily is normal. Many doctors are not aware that giving 5% dextrose is virtually giving free water which can induce or aggravate severe hyponatremia.
4. Hypokalemia is easier to treat than to prevent
5. All solutions containing amino acids & glucose are classified as PN.
6. All patients with low BMI* would require high calories and protein for repletion even though it is anticipated that they will resume oral intake within one week

*BMI = body mass index (Weight [kg] : Height [m]²)

I. RATIONALE FOR MAINTENANCE FLUID THERAPY

There are various reasons that the following situation are unraveled to attending physicians:

- Majority of patients are already in moderate dehydration, but their hemodynamics are not severely compromised. Some patients may already have had insufficient oral fluid intake before hospitalization or fever which cause increased insensible water loss.
- Anxiety, depression or fear. These tend to occur when a patient has tried to seek outpatient

treatment but his/her condition failed to improve or get worse..

- Malaise or fatigue may be the reason why the relatives bring the patient to hospital.
- Unfamiliarity or dislike of hospital food
- Insufficient oral intake (too weak to chew or bitter dry tongue)
- Inflexible mealtimes
- Anorexia, nausea, or distress
- Suppressed level of consciousness.

Such information may be overlooked, while at the same time patients need maintenance support.

Goal of maintenance fluid therapy can be summarized as follows:

1. Fulfills daily physiological requirements for homeostasis
2. Prevents electrolyte & acid base disorders
3. Supports primary therapy of patients' illness
4. Enzymatic process & protein synthesis
5. Facilitates recovery

What are the features of a good maintenance solution?

- Practical, easy and safe to administer
- In addition to basic electrolytes (Na^+ , K^+ , Cl^-) also contains microminerals (Mg^{++} , Ca^{++} , P) which are required for cellular metabolism
- The presence of value added zinc helps to promote tissue healing
- Contains high quality amino acids (BCAA enriched, high in EAA) to promote protein synthesis
- Glucose to maintain euglycemia

One of possible candidates to fulfill the above criteria is Aminofluid[®]. Compositions of Aminofluid and other

maintenance solution (KAEN3B) and Ringer's lactate are shown below:

Table 1. Composition of Aminofluid compared with Ringer's Lactate & KAEN3B

Composition	Aminofluid [®]	KAEN3B [®]	Ringer's lactate	ASPEN guideline ⁽²⁾
Water	2000	2000	2000	30-40 ml/kg/day
Na ⁺	70	100	260	1-2 mEq/kg/day
K ⁺	40	40	8	1-2 mEq/kg*/day
Cl ⁻	70	100	218	as needed
Mg ⁺⁺	10	-	-	8-20 mEq/day
Ca ⁺⁺	10	-	-	10-15 mEq/day
P	20	-	-	20-40 mEq/day
Zn	10 µmol	-	-	2.5-5 g
Amino acid	AA 60 g	-	-	0.8 g/kg/day≠
Glucose	150 g ¥	54 g	-	

* basic requirement for K⁺ homeostasis 20-30 mEq/daily⁽¹⁰⁾; ≠ basal amino acid requirement in nonstressed patients; ¥ protein-sparing effect

Why are microminerals also necessary?

In addition to basic minerals, such as sodium, potassium, chloride, today's maintenance solution should contain microminerals which are required for cellular metabolism. The role and recommended dosage are given in following table 2:

Table 2. Functions and recommended daily intake of water, electrolytes

	Functions ⁽³⁾	ASPEN* ⁽²⁾	Aminofluid
Water(ml)	Essential component of cells and other fluid compartments, temperature regulation, solvent, lubricant	30-40 ml/kg	2000
Na ⁺ (mEq)	In combination with chloride to maintain blood volume and osmolarity, regulate charging potential in neuromuscular junction, and influence acid-base balance	1-2 mEq/kg	70

K ⁺ (mEq)	Neuromuscular excitability, protein and collagen synthesis, enzymatic process in cellular energy production. In combination with sodium and calcium also maintains normal heart rhythm. Part of body's buffer system	1-2 mEq/kg	40
Cl ⁻ (mEq)	Along with sodium maintains osmolarity of ECF. Maintain fluid balance. Maintain acid-base balance. Exchange of oxygen and carbodioxide in red blood cells. Component of gastric juice	as needed to maintain acid-base balance	70
Mg ⁺⁺ (mEq)	Extremely important for enzyme systems. Neuromuscular activities. Essential for proper metabolism of ATP, Na ⁺ -K ⁺ pump. Facilitate neuromuscular integration and stimulate secretion of parathyroid hormone. Cardiac function.	8-20	10
Ca ⁺⁺ (mEq)	Proper development of bones and teeth, neuromuscular function, blood clotting ability, acid-base balance, and activation of certain enzymes	10-15	10
P(mmol)	essential for metabolism of nutrients such as carbohydrate, lipids and protein. Co-factor in numerous enzyme systems of cellular metabolism. ATP. Crucial component of DNA. Formation of bones. Acid-base regulation.	20-40	20

Zinc is one of essential trace elements provided in today's maintenance solution

	Functions	Urinary excretion	Aminofluid
Zinc	Promote wound healing. Zinc is necessary for the formation of collagen, which is essential material for tissue healing and repair. Zinc also provides	7.6 micromol/day	10 micromol/L

	immunity against disease. Required for metabolism of nutrients such as carbohydrates, protein, fat, and synthesis of nucleic acids (DNA and RNA)		
--	---	--	--

Why should we provide BCAA (branched-chain amino acids) in maintenance solution?

Leucine, isoleucine and valine are three amino acids most frequently studied and proven to have some pharmacological effects ^(4,5,6,7,8):

- Important precursors in the synthesis of glutamine and alanine in skeletal muscle
- Increased consumption of BCAA occurs in many illnesses
- Leucine positively affects protein synthesis in experimental model of sepsis and burns
- BCAA improves appetite by competitively block the entry of tryptophan, precursor of serotonin, into central serotonergic nervous system. Therefore, the decrease in serotonin level will reduce the stimulation of melanocortin system in the hypothalamus, followed by improved appetite (shown in the figure C below)

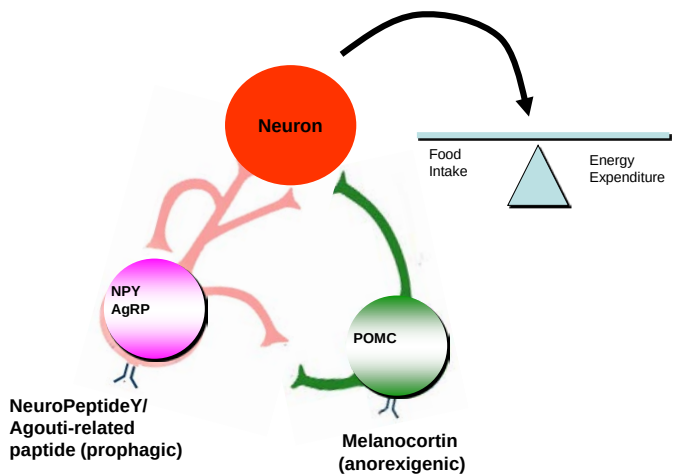


Fig A. Two systems exist in the hypothalamus. Melanocortin (Pro-opiomelanocortin) is a serotonergic system, the stimulation of which will result in anorexia. On the contrary, NPY is prophagic, meaning stimulation of which will result in increased appetite. Interplay of the two systems will control the balance of food intake and energy expenditure.

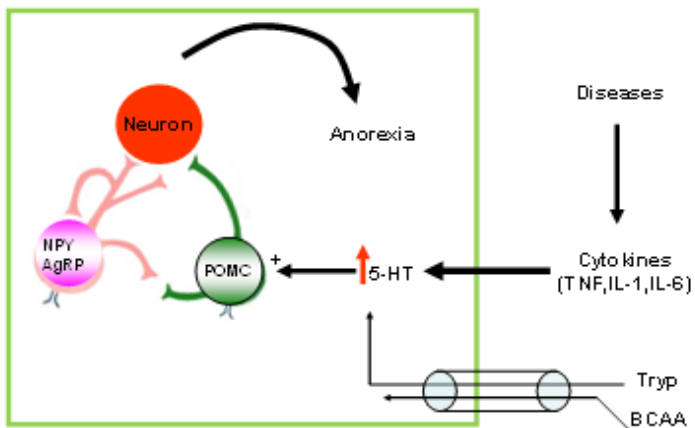


Fig B. In many systemic diseases cytokines will be produced, and these will increase serotonergic stimulation of melanocortin. This will contribute to anorexia. Serotonin is derived from aromatic amino acid, tryptophan which shares the common channel with BCAA to enter central nervous system. There is also evidence that increased tryptophan level in CNS will cause central fatigue.

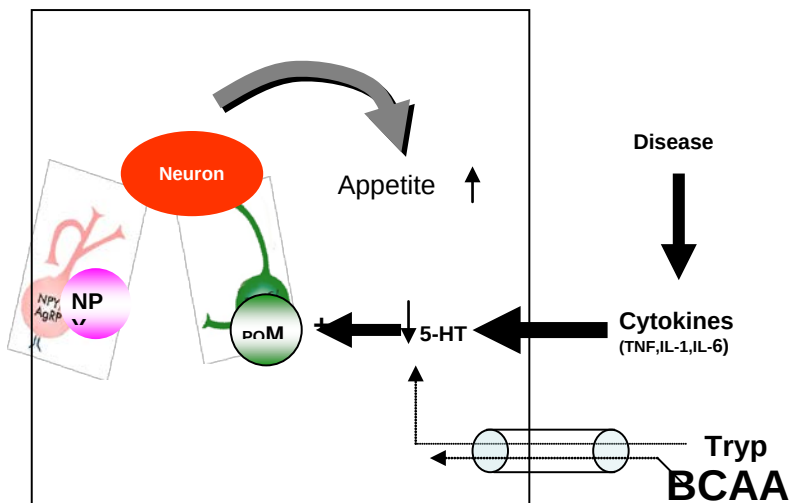


Fig C. Administration of BCAA (leucine, isoleucine, valine) will competitively outnumber and block the entry of tryptophan, followed by decreased serotonin level and hence increased appetite.

- In septic encephalopathies the BCAA to AAA ratio decreases
- Patients surviving sepsis had higher concentrations of the branched chain amino acids
- BCAA promotes cerebral blood flow

II. HOW DOES MAINTENANCE SOLUTION DIFFER FROM PARENTERAL NUTRITION?

Although no clear-cut definition exists, based on the importance of the constituents of infusion solutions, we can arbitrarily categorize a product as maintenance solution when the water and electrolyte components predominate whereas amino acids, glucose content serves to provide merely basic maintenance requirements and not to replete protein and energy loss. On the contrary, the prioritized contents of parenteral nutrition are amino acids or NPC (nonprotein calories as either carbohydrate or lipid).

HOW TO ADMINISTER MAINTENANCE SOLUTIONS

- Cannulation site: solutions having osmolality of less than 900 mOsm/L can be given via peripheral vein. However, more proximal vein (basilica, cephalic or median cubital) should be chosen because of higher incidence of phlebitis of dorsal hand vein. Elderly patients are more prone to phlebitis compared to young adults.
- Rate of administration: in general 20 drops per minute is the usual maintenance rate. However, one should account for the glucose & potassium concentration of individual products. In adults, maximum rate of glucose administration is 4 mg/kg/minute ⁽⁹⁾, and potassium being 10 mEq per hour. Although general recommended daily intake of potassium is 1-2 mEq/kg, minimum maintenance adult dose for homeostasis can be fulfilled by 20-30 mEq daily. ⁽¹⁰⁾
- Injectable drugs must not be admixed to maintenance solutions such as Aminofluid, because they can increase the osmolality and might disturb the stability of the composition. When deemed necessary an injectable drug can be administered by piggy bag (continuous drip) or stop cork (bolus) while temporarily turning off the primary flow of maintenance fluid.

III. HOW TO ASSESS THE BENEFITS OF SUPPORTIVE THERAPY

Success or failure of treatment cannot be attributed to a single modality. Supportive therapy serves to facilitate the outcome of the primary therapy.. It is impossible to study comparative efficacy of maintenance solutions because of many confounding factors. Some scoring systems have been developed to evaluate subjective conditions, such as fatigue score, appetite and activities of daily living

IV MONITORING AND POTENTIAL COMPLICATIONS

Monitoring is utmost important in maintenance fluid therapy. When there is laboratory facility, ideally electrolyte and metabolic panel (Na^+ , K^+ , Cl^- , HCO_3^- , BUN, glucose, creatinine)⁽¹¹⁾ should be checked prior to fluid administration because it is the best guide for selection of infusion solution. Given the presence increasing reports of electrolyte disorders, one should check and monitor at least Na^+ and K^+ . It is inappropriate to give hypotonic solution to hyponatremic patients⁽¹⁾. On the other hand, it is ridiculous to give isotonic saline to hypernatremic patients⁽¹²⁾. When necessary, maintenance solutions (Aminofluid) can be combined with replacement solution (Asering, RL, Normal saline) as well as parenteral nutrition products.

Hypokalemia is prevalent in hospitalized patients and should be prevented. The importance of potassium in maintenance solutions is reflected by reported prevalences of hypokalemia in some hospitals where hospitalized patients were given replacement solutions containing 4 mEq/L of K^+ (Ringer's lactate) or 0 mEq of K^+ (Normal Saline)

Chief Investigator	Centre	No of patients	% hypokalemia on admission	% hypokalemia on Discharge
Untung Sudomo ⁽¹³⁾	RSPAD	100	28	45
Djoko Widodo ⁽¹⁴⁾	RSCM	105	22.9	52.4
Nasronudin ⁽¹⁵⁾	RS Sutomo	110	36.36	50.91

Hyperkalemia can be induced or aggravated when giving potassium containing solutions to patients with anuria and oliguria.

CONCLUSION

- Good supportive therapy facilitates recovery
- Maintenance fluid therapy has evolved from simply giving water and electrolyte in simple container to practical and complete composition in advanced dual-chamber formulation
- Most important goal of maintenance therapy is to correct homeostasis, improve sense of well-being, combat fatigue, increase appetite and finally speed up recovery
- The role of Branched chain amino acids (Leucine, Isoleucine and Valine) is increasingly recognized.
- Recent findings suggest that BCAA can increase appetite and promote protein synthesis in skeletal muscle
- Amino fluid is not aimed to replete energy and protein
- Amino fluid is today's maintenance infusion solution, NOT peripheral parenteral nutrition or hypocaloric feeding
- When deemed necessary, Amino fluid can be combined with other electrolyte solutions (RA, RL, NS, KAEN) or Parenteral Nutrition products.

References:

1. Shafiee M.A.S., Bohn D, Hoorn EJ and Halperin ML. How to select optimal maintenance intravenous fluid therapy. Q J Med 2003; 96: 601-610
2. ASPEN Board of Directors and the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. JPEN Vol 26, No1 Suppl Jan-Feb 2002.
3. Lee, Carla A.B. Fluids and Electrolytes: a practical approach. 4 ed. FA Davis Philadelphia.
4. Alessandro Laviano; Michael M Meguid; Akio Inui; Maurizio Muscaritoli; Filippo Rossi-Fanelli. Therapy Insight: Cancer Anorexia-Cachexia Syndrome-When All You Can Eat Is Yourself. Nat Clin Pract Oncol. 2005;2(3):158-165.
5. Rossi-Fanelli et al. Branched Chain Amino Acids: The best compromise to achieve anabolism. Curr Opin Clin

- Nutr Metab Care 8:408-414. 2005 Lippincott Williams & Wilkins.
6. Jean-Pascal De Bandt and Luc Cynober Therapeutic Use of Branched-Chain Amino Acids in Burn, Trauma, and Sepsis. *J. Nutr.* 2006 136: 308S-313S
 7. Samuel N. Cheuvront, Robert Carter, III, Margaret A. Kolka, Harris R. Lieberman, Mark D. Kellogg, and Michael N. Sawka. Branched-chain amino acid supplementation and human performance when hypohydrated in the heat *J Appl Physiol*, Oct 2004; 97: 1275 - 1282.
 8. Calder PC. Branched-chain amino acids and immunity. *J Nutr.* 2006 Jan;136(1 Suppl
 9. Mizock BA, Troglia S. Nutritional support of the hospitalized patient. *Mosby Vol 53, No 6, 1997, p 367*
 10. Tannen RL. Potassium Disorders. In Kokko & Tannen : *Fluids and Electrolytes. 3rd Edition WB Saunders 1996. p 114*
 11. Mark Graber. Terapi Cairan, Elektrolit dan Metabolik. *Farmedia, 2003. p 95*
 12. Fiona REID*, Dileep N. LOBO*, Robert N. WILLIAMS*, Brian J. ROWLANDS* and Simon P. ALLISON† (Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study. *Clinical Science (2003) 104, (17–24)*
 13. Sudomo, Untung. Marissa Ira. *Gastroenterogy hepatology and digestive endoscopy vol.5. Ed: Dec 2004. Page: 115-120*
 14. Widodo D, Setiawan B, Khie Chen. The prevalence of hypokalemia in hospitalized patients with infectious diseases problems at Ciptomangun-kusumo Hospital Jakarta. *Acta Med Indones, 2006;38(4):202-5*
 15. Nasronudin et al. The Prevalence of hypokalemia and Hyponatremia in Infectious Diseases Hospitalized Patients. *Medika 2006 Vol XXXII, No 12, p 732-734*

WHY IS PROVISION OF AMINO ACIDS IMPORTANT DURING INFECTION?

Iyan Darmawan

Introduction

The interaction between nutrition and infection is complex. The physiological mechanisms responsible for metabolic changes during infection are not completely understood, although cytokines are clearly involved. Some degree of appetite loss (anorexia) is present during most infections. In some cases, this anorexia is due to nausea and vomiting; in others, gastrointestinal lesions. Additionally, the presence of a fever can result in appetite loss (anorexia) resulting in a 10–40% decrease in dietary intake, not only of protein and energy but also of most nutrients. Anorexia will precipitate clinical nutrient deficiencies of any nutrient in which body stores are limited. The extent of the depletion of nutrient status will subsequently increase the risk of damage to the host's tissues from the inflammatory response. To sustain a hypermetabolic rate (i.e., in fever), there is an acute mobilization of endogenous energy stores (glucose and fat). However, during infections, there is also an impaired ability to use these substrates. If body stores are used to provide for the metabolic needs of infection and fever, weight loss occurs. In fact, this sort of observation led to the introduction of the lay-term 'consumption' to describe tuberculosis, the classic chronic wasting infectious disease. The high prevalence of infections among children living in poor areas of developing countries results in impaired linear growth. In addition, the acute phase response (e.g., proinflammatory cytokine release) to fever directly affects bone remodeling that is required for long bone growth. ⁽¹⁾

The Cycle of Malnutrition and Infection

Malnutrition and infection interact in a cycle of adverse events (Figure 1) whereby malnutrition impairs

immunocompetence by affecting both nonimmunological defense mechanisms (such as epithelial membrane integrity) and immunological defenses (e.g., cytokine activity, neutrophil function, T-cell maturation) thereby increasing host susceptibility to infection. Conversely, infection can affect energy requirements and appetite, and can lead to weight loss in adults and growth disturbance in children⁽²⁾

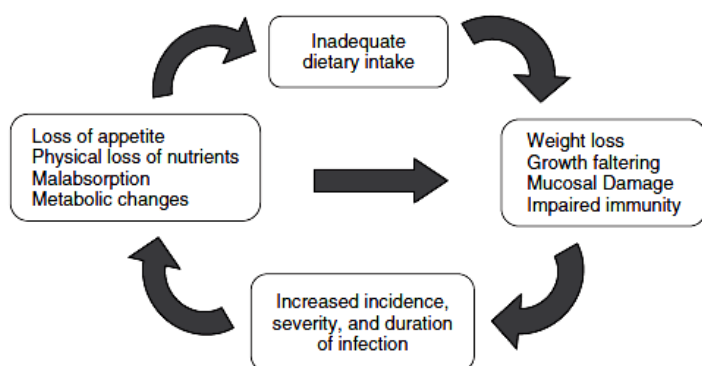


Figure 1. *The cycle of malnutrition and infection (Reproduced from Tomkins A and Watson F (1989). Malnutrition and Infection: A Review. Nutrition Policy Discussion Paper No.5 (ACC/SCN State of the Art Series). Geneva. United Nations (Klassen))*

Plasma free amino acid (PFAA) profiles have been reported over the past decades for healthy subjects and for patients with various diseases, including the lack of BCAA (branched chain amino acids) in patients with COPD⁽³⁾. The free amino acid pool represents only a small fraction of the total-body free amino acid content; concentrations in the intracellular space are considerably higher than plasma concentrations and most free amino acids are located in muscle tissue. However, PFAA concentrations might be of great value in reflecting changes in organ nitrogen handling and altered amino acid metabolism.

Role of Amino acids during infection

During inflammation and infection, protein metabolism is distinctly altered. This alteration is directly due to a flux of amino acids from peripheral tissues, primarily skeletal muscle, into the liver. Amino acids are utilized in the synthetic pathways of arginine and glutathione and in lymphocyte and acute-phase protein. In fact, a decrease in almost all PFAA concentrations is observed during acute infection, the exception being concentrations of phenylalanine. ⁽⁴⁾

The relations between the concentrations of some PFAAs, such as the molar ratio of phenylalanine to tyrosine (Phe:Tyr; 13) and the Fischer molar ratio [(valine + leucine + isoleucine)/ (phenylalanine + tyrosine)], may prove to be important informative indexes for distinguishing malnutrition from infectious processes. The glycine-to-valine index is used to distinguish malnutrition from catabolic stress. ⁽⁴⁾

Aminogram in Dengue Infection

Klassen et al compared plasma from the 2 populations sampled in Guatemala analyzed in the same laboratory as was the control material from Sweden. Because no significant differences between the healthy Guatemalan subgroups were found, they combined these into one group for comparison with the patients with dengue. For comparison of the Guatemalan control subjects with either the Swedish adults or the patients with dengue, they used data for the Guatemalan control group from the first examination day. Compared with the healthy Guatemalan adults, patients with dengue had lower total PFAA concentrations and lower nonessential amino acids concentrations at time point 1

		Guatemalans	
Amino acid	Swedish reference group ² (n=27)	Healthy (n=22)	Patients with dengue (n=17)
Essential		$\mu\text{ mol/L}$	
Histidine	87 ± 3	87 ± 6	67 ± 3^3
Isoleucine	63 ± 3^3	53 ± 3	49 ± 3
Leucine	120 ± 5^3	105 ± 6	95 ± 6
Lysine	195 ± 9	150 ± 8	126 ± 10
Methionine	25 ± 1^3	24 ± 1	25 ± 2
Phenylalanine	53 ± 2	50 ± 3	75 ± 8^3
Threonine	128 ± 5^3	108 ± 5	80 ± 6
Tyrosine	60 ± 4	54 ± 2	50 ± 3
Tryptophan	46 ± 3^3	34 ± 2	28 ± 3
Valine	220 ± 8^3	182 ± 11	162 ± 8
Nonessential			
Alanine	316 ± 17	340 ± 17	274 ± 24^4
Arginine	86 ± 3^4	69 ± 3	63 ± 5
Asparagine	47 ± 2^4	40 ± 2	36 ± 2
Citrulline	34 ± 1	24 ± 2	21 ± 2
Glutamic acid	32 ± 4	36 ± 20	37 ± 3
Glutamine	655 ± 17^3	511 ± 4	467 ± 23
Glycine	248 ± 13	210 ± 17	171 ± 13
Ornithine	66 ± 4^3	41 ± 3	38 ± 3
Serine	114 ± 4^4	102 ± 5	86 ± 7
Taurine	49 ± 3^4	36 ± 22	41 ± 9
BCAA	438 ± 21^3	337 ± 20	312 ± 17
□ EAA	857 ± 27	841 ± 38	726 ± 65
□ NEAA	1446 ± 38	1435 ± 49	1121 ± 57^4
□ TAA	2303 ± 58	2342 ± 88	1847 ± 116^4
Ratios			
Phe: Tyr	0.96	0.94	1.54^3
Fischer's ratio	3.57	3.26	2.46^3
Gly:Val	1.13	1.20	0.93

¹ $\bar{x} \pm \text{SEM}$. BCAA, branched-chain amino acids; EAA, essential amino acids; NEAA, nonessential amino acids; TAA, total amino acids; FR, Fischer molar ratio.

²Data from Divino-Filho et al

^{3,4}Significantly different from healthy Guatemalan control subjects (ANOVA and Dunnett's test): ³ $P < 0.01$, ⁴ $P < 0.05$.

One study reported that in sepsis, virtually all amino acid levels were decreased by 10-30% (p less than 0.05), whereas cystine and phenylalanine were significantly elevated. The two other aromatic amino acids (AAA) tryptophan and tyrosine are frequently elevated. The BCAA concentrations are most often decreased. These changes were more pronounced in severe sepsis. ⁽⁵⁾

Fatigue in Patients with Dengue Hemorrhagic Fever

Post-infectious fatigue was observed in approximately 25% of hospitalized patients with dengue infection. Poor appetite, fatigue and nausea might be important cause of decrease oral intake during illness. ⁽⁶⁾

Conclusion

It is reasonable to provide at least basal requirement of amino acids in patients with acute infectious diseases, particularly those with insufficient oral intake. In infection, the role of cytokines, fever, dehydration in causing anorexia is well established. Therefore, provision of amino acids, glucose on top of basic electrolytes (such as Aminofluid ®) should be considered a novel trend in parenteral fluid therapy for patients with infectious diseases.

Reference:

1. Field CJ. Infection, fever and nutrition. Encyclopedia of Food Sciences and Nutrition. 2nd edition 2005. pp3307-3315
2. Ghattas H. INFECTION Nutritional Interactions Encyclopedia of Human Nutrition, 2005, Pages 47-54
3. Kutsuzawa T, Shioya S, Kurita D, Haida M .Plasma branched-chain amino acid levels and muscle energy metabolism in patients with chronic obstructive pulmonary disease Clinical Nutrition, Volume 28, Issue 2, April 2009, Pages 203-208
4. Klassen P, Furst P, Schulz C, Mazariegos M, Solomons NW. Plasma free amino acid concentrations in healthy

Guatemalan adults and in patients with classic dengue. Am J Clin Nutr 73: 647–652, 2001

5. Vente, J. von Meyenfeldt, M. van Eijk, H. Soeters, P. Plasma-amino acid profiles in sepsis and stress. Ann Surg. 1989 January; 209(1): 57–62.
6. Seet RCS, et al. Post-infectious fatigue syndrome in dengue infection. Journal of Clinical Virology Volume 38, Issue 1, January 2007, Pages 1-6

THE IMPORTANCE OF MAGNESIUM IN HOSPITALIZED PATIENTS

Iyan Darmawan

Introduction

Magnesium (Mg^{++}) is the second most abundant intracellular cation after potassium present in living cells. Of the 21–28 g of Mg present in the adult human body, 99% is distributed in the intracellular compartment, and only 1% in the extracellular fluid. Mg is subdivided into three major compartments of the body: about 65% in the mineral phase of skeleton, 34% in the intracellular space, and only 1% in the extracellular fluid. Small intestine is the main site for Mg absorption, whereas Mg excretion is mainly performed through renal pathways. Serum Mg exists in three forms: a protein-bound fraction (25% bound to albumin and 8% bound to globulins), a chelated fraction (12%), and the metabolically active ionized fraction (Mg^{++} : 55%). The levels of Mg in the plasma of healthy people are extremely constant, with a reference interval for total serum levels of 0.75–0.96mmol/L, and a mean of 0.85mmol/L.⁽¹⁾

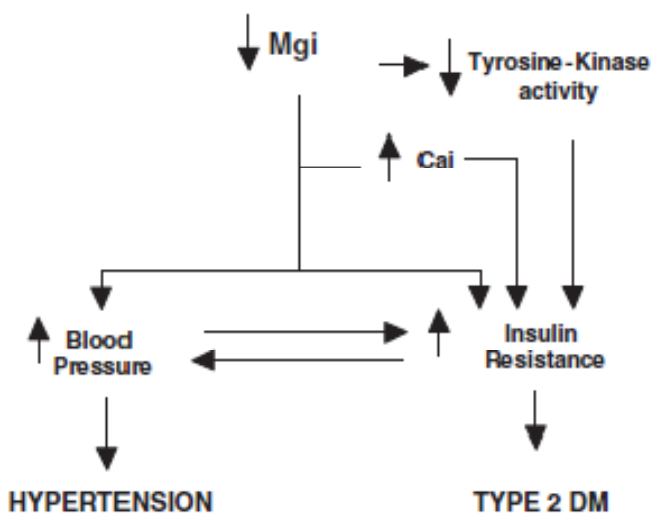
On the other hand, magnesium deficiency in hospitalized patients is more prevalent than previously thought. Approximately 10% of patients admitted to large city hospitals are hypomagnesemic and this incidence may increase to as high as 65% in medical intensive care units (2,3). Thus, previous belief that magnesium should be provided in maintenance solution only after prolonged hospital stay (e.g. > 7 days) may no longer be true. Instead, magnesium and also other microminerals and trace elements should be provided early in view of the prevalent “magnesium wasting” illnesses, such as gastrointestinal disorders (acute and chronic diarrhea, regional enteritis, ulcerative colitis, malabsorption etc), “magnesium wasting” drugs (diuretics, aminoglycosides,

cisplatin) and endocrine disorders (diabetes, hyperparathyroidism, hyperthyroidism).

Hypomagnesemia in diabetes mellitus

Diabetes mellitus is perhaps the most common disorder associated with Mg deficiency. Up to 39 percent of outpatient diabetics have been reported to be hypomagnesemic. ^(2,3) In severe ketoacidosis, Mg may be wasted into the urine during the acidosis. The serum Mg concentration may be normal or high owing to volume depletion; however fluid and insulin therapy usually results in a fall into subnormal range. Insulin has been demonstrated to cause a shift of Mg into soft tissue. The lack of insulin in type 1 diabetes could result in a decrease in intracellular Mg.

Despite the deduction that the hypomagnesemia is caused by the diabetes and not the opposite, the Mg deficiency also can influence in the onset of this disease. The Mg deficit interferes on enzymatic reactions that use or produce adenosine triphosphate (ATP), in consequence modifies the enzymatic cascade that involves the carbohydrates metabolism, triggering DM. Mg deficiency may result in disorders of tyrosine-kinase activity on the insulin receptor, event related to the development of insulin resistance and decreased cellular glucose utilization ⁽⁴⁾



Magnesium depletion in gastrointestinal disorders

The Mg content of upper intestinal tract is approximately 1 mEq/L. Vomiting and nasogastric suction, may therefore contribute to Mg depletion. The Mg content of diarrheal fluids and fistulous drainage is much higher (up to 15 mEq/L). Consequently, Mg depletion is common in acute and chronic diarrhea, regional enteritis, ulcerative colitis and intestinal and biliary fistulas.

Malabsorption syndrome due to nontropical sprue, radiation injury resulting from therapy for disorders such as carcinoma cervix, the intestinal lymphangiectasia may result in Mg deficiency. Other conditions resulting in magnesium depletion include steatorrhea, acute hemorrhagic or edematous pancreatitis and small bowel resection.

Conclusion

Magnesium in concert with other microminerals, such as calcium, phosphate and zinc should be considered in hospitalized patients with endocrine and gastrointestinal disorders. Patients with insufficient oral intake should be managed with proper parenteral fluid containing those

elements in addition to glucose and amino acids (eg Aminofluid ®). The objectives of maintenance fluid therapy are: 1) prevent dehydration and electrolyte disorder 2) prevent micromineral deficiency 3) prevent and treat ketoacidosis 4) minimize protein degradation and 5) afterall, it is indicated to accelerate recovery.

References

1. Rude RK. Magnesium Disorders. In Kokko and Tannen. Fluids and Electrolytes. WB Saunders Co.3rd ed. p 432-433.
2. Rude RK , Magnesium Homeostasis. Principles of Bone Biology, 3rd Edition Copyright © 2008
3. Barbagallo M & Dominguez LJ. Magnesium metabolism in type 2 diabetes mellitus, metabolic syndrome and insulin resistance. Archives of Biochemistry and Biophysics. Volume 458, Issue 1, 1 February 2007, Pages 40–47
4. Sales CH, Pedrosa LDFC . Magnesium and diabetes mellitus: Their relation. Clinical Nutrition (2006) 25, 554–562

SUPPORTIVE FLUID THERAPY IN DHF

Iyan Darmawan

Unlike many bacterial infectious diseases and parasitic diseases which require specific drug therapy, treatment of DHF depends merely on proper fluid management and monitoring. Correction of moderate dehydration due to fever, hyperventilation and decreased oral intake must be initiated, because in addition to improving general condition, it obviates the misinterpretation of hemoconcentration as a hallmark of capillary leakage.

In general, parenteral fluid therapy can be classified into three categories: Resuscitation, Repair and Maintenance. Since, severe electrolyte and acid-base disorders rarely complicate DHF, repair fluid therapy is seldom administered for DHF patients.

Hitherto, resuscitation fluid therapy is defined as giving isotonic infusion solution (lactated ringer's, acetated ringer's, 0.9% NaCl and/or colloid at high infusion rate to patient with hemodynamic derangement or hypovolemic shock ⁽¹⁾. The most common place is grade 3 and 4 , aka dengue shock syndrome. Given the widespread availability of isotonic infusion solutions, they are commonly given also to patients with grade 1 and 2 DHF, simply to satisfy the comfort level of the attending physicians that in leakage conditions isotonic solutions would be preferred although there are no strong reasons, except in mild hyponatremia.

Maintenance fluid therapy can be viewed as an important supportive therapy for hospitalized patients. Unlike resuscitation fluid therapy where the goal is to restore hemodynamic derangement, maintenance therapy is aimed at maintaining homeostasis in patients who have insufficient oral intake of fluid

Goal of maintenance fluid therapy can be summarized as follows:

1. Fulfills daily physiological requirements for homeostasis. Restore quickly the depleted fluid and electrolyte content of intracellular compartment
2. Prevents electrolyte & acid base disorders
3. Supports primary therapy of patients' illness
4. Enzymatic process & protein synthesis
5. Facilitates recovery

What are the features of a good maintenance solution ? ⁽²⁾

1. Practical, easy and safe to administer
2. In addition to basic electrolytes (Na^+ , K^+ , Cl^-) also contains microminerals (Mg^{++} , Ca^{++} , P) which are required for cellular metabolism
3. The presence of value added zinc helps to promote tissue healing
4. Contains high quality amino acids (BCAA enriched, high in EAA) to promote protein synthesis
5. Glucose to maintain euglycemia, prevent ketosis, and protein-sparing effects.

One of possible candidates to fulfill the above criteria is AminoFluid[®]. Compositions of AminoFluid[®] and other maintenance solution (KAEN3B[®]) and Ringer's lactate are shown below:

Table 1. Composition of AminoFluid compared with Ringer's Lactate & KAEN3B

Composition	AminoFluid [®]	KAEN3B [®]	Ringer's lactate	ASPEN guideline ⁽²⁾
Water	2000	2000	2000	30-40 ml/kg/day
Na^+	70	100	260	1-2 mEq/kg/day
K^+	40	40	8	1-2 mEq/kg*/day
Cl^-	70	100	218	as needed

Mg ⁺⁺	10	-	-	8-20 mEq/day
Ca ⁺⁺	10	-	-	10-15 mEq/day
P	20	-	-	20-40 mEq/day
Zn	10 µmol	-	-	2.5-5 mg
Amino acid	AA 60 g	-	-	0.8 g/kg/day [≠]
Glucose	150 g ¥	54 g	-	

* basic requirement for K⁺ homeostasis 20-30 mEq/daily ⁽¹⁰⁾; [≠] basal amino acid requirement in nonstressed patients; ¥ protein-sparing effect

Maintenance IV fluid therapy can be considered to substitute the oral intake of water and nutrients. Its place in grade 1 and 2 must be encouraged when oral intake is severely impaired by nausea, anorexia and vomiting. The rationale of new generation maintenance solution as supportive fluid therapy in grade 1 & 2 DHF is based on the following:

1. Although patients feel thirsty due to probable hypertonic dehydration, they might not be able to consume enough water and nutrient owing to abdominal discomfort/pain, hepatomegaly
2. Elevated levels of cytokines, such as interferons (IFNs), interleukin-2 (IL-2), IL-8, and tumor necrosis factor alpha, have been reported in DHF⁽³⁾ One of their pleiotropic effects is delaying gastric emptying
3. Patients might experience loss of appetite because of dry mouth (dehydration), malaise and fatigue besides other systemic symptoms⁽⁴⁾.

Therefore, once body fluid homeostasis is restored, systemic symptoms might be alleviated and further progression to more severe illness is prevented.

* Abstract from Proceedings of Lunch Symposium Advances in Maintenance Fluid Therapy in medical Patients. The 5th International Symposium and the 8th International Course on Metabolism and Clinical Nutrition (ISCMCN) FKUI 2010

References:

1. Prevention and Control of Dengue and Dengue Haemorrhagic Fever. WHO Regional Publication, SEARO No 29.
2. Darmawan I. Paradigma Baru dalam Terapi Cairan Maintenance. Simposium Nasional Penyakit Tropik Infeksi, HIV & AIDS, J W Marriott Hotel, Surabaya 22 Maret 2008
3. Anon Srikiatkachorn, Chuanpis Ajariyakhajorn, Timothy P. Endy, Siripen Kalayanaroj, Daniel H. Libraty, Sharone Green, Francis A. Ennis, and Alan L. Rothman Virus-Induced Decline in Soluble Vascular Endothelial Growth Receptor 2 Is Associated with Plasma Leakage in Dengue Hemorrhagic Fever J Virol. 2007 February; 81(4): 1592–1600.
4. Othman N. Clinical profile of dengue infection in children versus adults. International Journal of Antimicrobial Agents, Volume 29, Supplement 2, March 2007, Page S435

NEW PARADIGM IN POSTOPERATIVE MAINTENANCE FLUID THERAPY

Iyan Darmawan

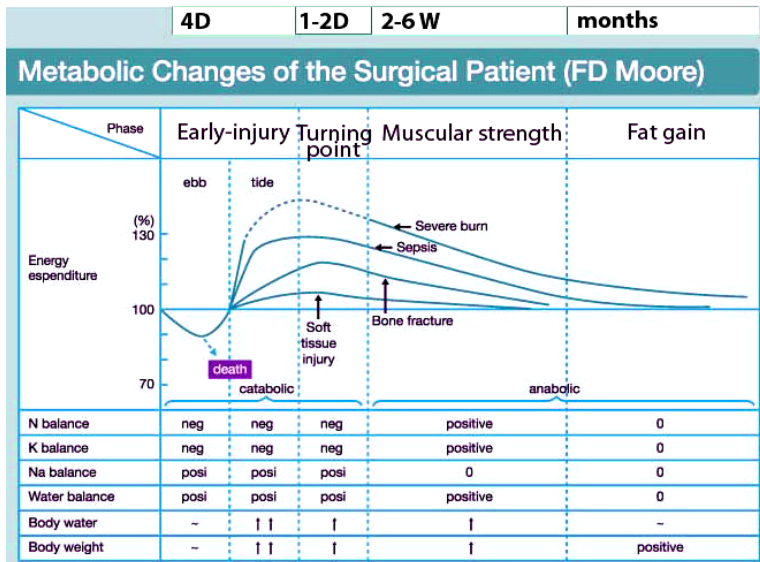
Introduction

Traditionally, many patients undergoing major gastrointestinal resections receive large volumes of crystalloids intravenously during and after surgery. It was suggested that fluids and electrolytes were given in excess, resulting in substantial weight gain and edema. It was also suggested that this overload was a major cause of postoperative ileus and delayed gastric emptying⁽¹⁻²⁾. When fluids were restricted to the amount needed to maintain salt and water balance, gastric emptying returned sooner and patients were capable of tolerating normal food and had bowel movements several days earlier than those in positive balance.

The main goals of postoperative maintenance support are to enhance postoperative recovery, to maintain fluid and electrolyte balance

Rationale of postoperative moderate volume and sodium administration

It has been long recognized that surgery, like any injury to the body, triggers a series of reactions including release of stress hormone and anti-inflammatory mediators. Aldosterone and ADH released in response to surgical stress might induce water retention and cause water and sodium positive balance during early injury.



Source: Harumasa Ohyanagi, the significance and recent advances In perioperative intravenous fluid Management ESPEN Meeting 2008

Therefore, urine output during initial postoperative period do not necessarily reflect hydration status.

Fatal postoperative pulmonary edema was reported to occur within 36 hours postoperatively when net fluid retention exceeds 67 ml/kg/day on average.⁽³⁾ Moreover, Water and sodium excretion tends to be slow after infusion of higher sodium containing solution⁽⁴⁾. These have prompted the recommendation of administering a maximum of 2 liters of fluid postoperatively and sodium of less than 60 to 100 mmol/day.⁽¹⁾ Low sodium does not aggravate the interstitial fluid expansion in patients with hypoalbuminemia which may delay surgical wound healing⁽⁵⁾.

Rationale of Low Glucose

Blood glucose concentrations increase after surgery begins. Cortisol and catecholamines facilitate glucose production as a result of increased hepatic glycogenolysis and gluconeogenesis. In addition, peripheral use of glucose is decreased.

Only half of the glucose infused at $4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ is directly oxidized after surgical or accidental trauma, and this percentage even falls when glucose is administered in higher doses ⁽⁶⁾

Blood glucose concentrations are related to the intensity of the surgical injury; the changes follow closely the increases in catecholamines. In cardiac surgery, blood glucose concentrations can increase up to 10–12 mmol/L (180–216 mg/dl) and remain elevated for >24 h after surgery. The changes are less marked with minor surgery ⁽⁷⁾

The usual mechanisms that maintain glucose homeostasis are ineffective in the perioperative period. Hyperglycaemia persists because catabolic hormones promote glucose production and there is a relative lack of insulin together with peripheral insulin resistance.

Although, the commonly used formula of 25 kcal/kg ideal body weight furnishes an approximate estimate of daily energy expenditure and requirements and under conditions of severe stress requirements may approach 30 kcal/kg ideal body weight ^(8,9), a rational approach during the early flow phase would be to provide 10 – 20 kcal/kg according to actual weight or adjusted weight if actual weight is > 120% of ideal body weight (IBW). After the stress response has resolved, caloric provision may be increased to meet measured or estimated energy requirements in normal-weight patients ⁽¹⁰⁾.

Protein/Amino acids

Amino acid requirements in postoperative period are higher when the patient is stressed/ traumatized/ infected than in the non-stressed state) as a consequence of the stressed body breaking down more protein and more essential amino acids than when nonstressed. One reason why this is a useful

arrangement is that it allows the immune system to increase its activity. For this purpose, more glutamine and alanine are required. They are produced by transamination of carbon skeletons with amino groups from the branched chain amino acids (BCAA) which are irreversibly degraded in this process and cannot be re-utilized for renewed protein synthesis. It is well established that muscle protein degradation is regulated by pro-inflammatory modulators like TNF- α , IL-6 and others, and therefore cannot be reversed by nutrition. The value of nutritional support comes instead from its support of protein synthesis in muscle and most importantly in the liver, yielding acute phase proteins, and in the immune system, yielding white cells crucial in the response to trauma or disease, and thereby limits net whole body protein loss.⁽⁸⁾ Basic amount of amino acids (30 g/L) is included in current maintenance solution.

Role of Aminofluid in surgical patients

Being a new generation maintenance solution, there are strong reasons for Aminofluid to be administered to patients after straightforward surgery, in order to enhance recovery.

- 10-20 kcal/kg ideal during flow phase, moderate supply of glucose prevents worsening of stress-induced hyperglycemia and insulin resistance
- Patients with mild to moderate stress and anticipated absence of oral intake of less than 7 days, require only 500-600 kcal/day
- Synchronous administration of BCAA-enriched amino acids and glucose in dual-chamber soft bag will improve nitrogen balance and postoperative fatigue
- Zinc to promote wound healing, support immune function, cellular growth and important in body antioxidant system

- Na^+ in moderate concentration prevent water retention and iatrogenic fluid overload; the presence of K^+ prevents further depletion of potassium

SUMMARY

In modern surgical practice, it is advisable to manage patients within an enhanced recovery protocol and thereby eating normal food after several days. This applies particularly for most surgical patients who are neither malnourished nor complicated by infection/sepsis. Consequently, there is little room for routine perioperative artificial nutrition, by which patients require “full dose” nutrition support. In this regards, all patients need during early postoperative period is a complete maintenance fluid therapy to improve surgical outcome and facilitate recovery.

Reference:

1. Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. *Lancet* 2002; 359: 1812-1818.
2. MacKay G, Fearon K, Mc Connachie A, Serpell MG, Molloy RG, O'Dwier PJ. Randomized clinical trial of the effect of postoperative intravenous fluid restriction on recovery after elective colorectal surgery. *Br J Surg*, 2006; 93: 1469-1474
3. Arieff Allen L. Fatal Postoperative Pulmonary Edema. Pathogenesis & Literature Review. *CHEST* 1999;115:1371-1377
4. Fiona REID, Dileep N. LOBO, Robert N. WILLIAMS, Brian J. ROWLAND Sand Simon P. ALLISON (Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study *Clinical Science* (2003) 104, (17–24)
5. Hill G.L. Disorders of nutrition and metabolism in clinical surgery. Churchill Livingstone 1990

6. Schricker T, Lattermann R, Schreiber M, Geisser W, Georgieff M, Radermacher P. The hyperglycaemic response to surgery: pathophysiology, clinical implications and modification by the anaesthetic technique. *Clin Intensive Care* 1998; 9: 118–28.
7. J. P. Desborough. The stress response to trauma and surgery. *British Journal of Anaesthesia*, 2000, Vol. 85, No. 1 109-117
8. Braga M, et al. ESPEN Guidelines on Parenteral Nutrition: Surgery
9. Saito H. Perioperative Nutrition Support. *Nutr & Met Support in Clinical Practice*. 1998 Pensa.
10. Boitano M. Hypocaloric Feeding of the Critically Ill. *Nutrition in Clinical Practice*, ASPEN 2006; 21:617-622.

PARENTERAL FLUID THERAPY IN STROKE PATIENTS

Iyan Darmawan

Adequate fluid intakes must be ensured in stroke patients at risk of dehydration, especially in the presence of dysphagia and reduced consciousness^(1,5) Monitoring and attempting to stabilize acute physiological parameters within normal limits such as blood pressure, temperature, hydration status, glucose levels and oxygen saturation has become standard practice for some acute stroke units⁽¹⁾

Parenteral fluids may have reduced the occurrence of dehydration and maintained systemic blood pressure after acute stroke.⁽²⁾ Selection of initiating solutions during acute phase has been decided arbitrarily owing to the fact that studies of electrolyte imbalance after stroke are not extensive, and it remains unclear whether initial hydration status influences mortality or functional recovery. As a rule, rehydration with 5% dextrose or hypotonic solutions during the first hours is not justifiable since it will readily enter the brain cells resulting in worsening of brain edema. The American Heart Association has recommended normal saline at 50 ml/hour during the first hours of acute ischemic stroke⁽³⁾.

However, it is not stated clearly when one has to switch to maintenance solution. Anaerobic metabolism initiated by ischemia induces local lactic acidosis and elevated tissue PCO_2 (not necessarily systemic lactic acidosis)⁽⁴⁾. This fact has caused many authorities to decline the use of lactated Ringer's solution as 'resuscitating' solution in acute stroke. Secondly, the osmolality of lactated Ringer i.e. 273 is considered hypotonic to plasma (normally 285 ± 5 mOsm/L). Since there has been no standard fluid regimen, neurologists may either use normal saline, Ringer's solution or even some doctors use Ringer's lactate in spite of the concern. The proponents of Ringer's solution may either think that the osmolality of

Ringer's solution (310 mOsm/L) is ideal in preventing edema, or thought wrongly that Ringer's solution is the same as Ringer's lactate minus lactate. In fact, their sodium and chloride contents differ significantly⁽⁶⁾.

	Glu	Electrolyte(mEq/L)						
Product	Glu (g/L)	Na⁺	K⁺	Ca⁺⁺	Cl⁻	Lactate	Acetate	(mOsm/L)
Normal saline	-	154	-	-	154	-	-	308
Ringer's solution	-	147	4	4,5	155.5	-	-	310
Lactated Ringer (RL)	-	130	4	3	109	28	-	273
Asering (acetated Ringer)	-	130	4	3	109	-	28	273
KAEN 3B	27	50	20	-	50	20	-	290
KAEN 3A	27	60	10	-	50	20	-	290

Within the context of fluid resuscitation in hypovolemic shock, the prolonged use of normal saline and Ringer's solution is associated with increased risk of hyperchloremic dilutional acidosis. In head injuries or subarachnoid hemorrhage, the use of normal saline and Ringer's solution may be suitable in view of high incidence of electrolyte imbalances, particularly hyponatremia. Any intracranial disease, surgery, mechanical ventilation and anesthetics may be complicated with electrolyte imbalance. Two distinct entities exist, namely cerebral salt wasting and SIADH.

The former is truly sodium depletion and although the clinical picture is similar to latter, this condition (CSWS) requires different approach of management by which high sodium infusion solution is warranted⁽⁷⁾ On the contrary SIADH responds merely to fluid restriction in the region of 600-800 ml/day. However, this is not possible in critically ill who may require minimum fluid load more than this to maintain cerebral perfusion pressure.

These two conditions are the suitable indications for normal saline and Ringer solution.

However, it remains to be questionable if normal saline or Ringer's solution are suitable as maintenance solution in acute ischemic stroke. One should also consider that spurious hyponatremia may be caused by tremendous hyperglycemic response during acute phase.

Each 100 mg/dl increase of glucose concentration is associated with reduction of 1.7 mEq/L of sodium. In addition, plasma osmolarity is also important factor.

One recent study has shown that the raised plasma osmolarity during admission is associated with stroke mortality. Plasma osmolarity >296 is considered indicative of hyperosmolar state. This study however did not show the influence of intravenous rehydration, unlike beneficial oral rehydration on clinical outcome⁽²⁾ (note: type of infusion solution was not mentioned explicitly).

Ringer's acetate may be a suitable alternative to normal saline and Ringer's solution.

LR and AR differ only in their bicarbonate source. LR contains 28 mmol of lactate per liter while AR has 28 mmol of acetate. Unlike lactate the metabolism of which takes place mostly in the liver, acetate is metabolized mainly in muscles and to a lesser extent in kidneys and heart. Acetate Ringer's solution has become a standard resuscitation fluid in pediatric diabetic ketoacidosis, and proved to be a better intraoperative solution than LR in maintaining core temperature during iso- and sevofluran anesthesia^(8,9,10).

The issue of osmolarity can be solved by addition of 20% or 40% magnesium sulphate. For example, to render the osmolarity of Ringer's acetate to 290, add 10 ml of 20% MgSO_4 . Administration of MgSO_4 is at least safe in stroke patients.⁽¹¹⁾

Current Osmolarity of Asering (Ringer's acetate)	Desired osmolarity	ml of 20% MgSO ₄ to be added	Mg (mEq /cc)	Magnesium (total)
273.4	285	7.25		12 mEq
273.4	290	10.375		17 mEq
273.4	295	13.5	1.66	22.41 mEq
273.4	300	16.625	mEq/cc	27.5 mEq

Once the hemodynamic condition has been stabilized, maintenance fluid therapy can be given as KAEN 3B/KAEN 3A. These two solutions may offer advantages in hypertonic dehydration as well as providing daily homeostasis requirement of potassium and sodium. There has been increasing evidence a high potassium intake caused a large reduction in deaths from stroke even when blood pressure was precisely matched between those on the high and low potassium intakes⁽¹²⁾.

CONCLUSION:

Neurologists should not underestimate the importance of hydration status of stroke patients. One particular theme that has emerged from stroke unit trials is that there are differences in the way acute physiology (such as temperature, blood pressure, blood glucose and hydration) are managed between these units and nonstroke units.

There are different approaches of rehydrating patients with ischemic stroke from those with SAH, head injuries or neurosurgeries.

Timing and selection of parenteral fluids may need to be revisited. One good candidate for initiating solution in acute ischemic stroke is Ringer's acetate. Unlike normal saline or Ringer solution, it is not associated with increased risk of hyperchloremic dilutional acidosis when given aggressively in correcting dehydration and shock. Secondly, it does not interfere with the interpretation of focal (tissue) lactic acidosis. Should there be a desire to

approximate the osmolarity of Ringer's acetate to that of plasma, addition of 20% magnesium sulfate is enabled in view of its established safety, while there is now ongoing large scale efficacy study involving 712 patients. Following acute phase of stroke, maintenance solution can be considered to keep the electrolyte homeostasis, particularly potassium and sodium.

REFERENCES

1. Bhalla A, Wolfe CD, Rudd AG. management of acute physiological parameters after stroke. QJM 2001 Mar;94(3):167-72.
2. Bhalla A. et al. Influence of Raised Plasma Osmolality on clinical outcome after acute stroke. Stroke. 2000;31:2043-2048
3. Adams HP et al. Guidelines for the Early Management of Adults With Ischemic Stroke *Stroke* 2007, 38:1655-1711
4. William E. Hoffman, Fady T. Charbel,, Guy Edelman, James I. Ausman, Brain tissue acid-base changes during ischemia *Neurosurgical Focus* 2(5): Article 2, 1997
5. Whelan K. Inadequate fluid intakes in dysphagic acute stroke. *Clin Nutr* 2001 Oct;20(5):423-8
6. Pedoman Cairan Infus PT Otsuka Indonesia 2000
7. Springate J. Cerebral Salt-Wasting Syndrome. *eMedicine Journal*, may 2, 2001 Vol 2 No 5
8. Darmawan I. Ringer's acetate solution in clinical practice. *Medimedia* 1999
9. Kashimoto S. Comparative effects of Ringer's acetate and lactate solutions on intraoperative central and peripheral temperatures. *J Clin Anesth* 1998;10(1):23-27
10. Mark A Graber. Terapi Cairan, Elektrolit dan Metabolik. *Farmedia*. Edisi 3, 2010
11. Keith W. Muir, Keneddy R. Lees. Dose Optimization of Intravenous Magnesium Sulfate. (*stroke*.1998;29:918-923).
12. Feng J He, Graham A MacGregor, Beneficial effects of potassium *BMJ* 2001;323:497-501 (1 September)

STRESS HYPERGLYCEMIA IN PATIENT WITH ACUTE STROKE: LET IT BE OR TAKE ACTION ?

Iyan Darmawan,

Introduction:

Hyperglycemia will be detected in about one third of patients with stroke and can cause detrimental effects of increasing tissue lactic acidosis, secondary to anaerobic glycolysis and free radical production ⁽¹⁾. After stroke of either subtype (ischemic or hemorrhagic), the unadjusted relative risk of in-hospital or 30-day mortality associated with admission glucose level >6 to 8 mmol/L (108 to 144 mg/dL) was 3.07 (95% CI, 2.50 to 3.79) in nondiabetic patients and 1.30 (95% CI, 0.49 to 3.43) in diabetic patients⁽²⁾. A good understanding on the pathophysiology and management of stroke hyperglycemia is essential, particularly before one considers administering glucose containing parenteral solutions, e.g. Aminofluid and KAEN 3B.

Definition of hyperglycemia

The concept of stress-induced hyperglycemia, typically defined as BG concentrations > 200 mg/dl has been described for almost 150 years ⁽³⁾. Various studies assessing relative risk of 30-day mortality associated with stress hyperglycemia in stroke patients had used a considerable diversity of cut-offs fasting or random glucose levels⁽²⁾. For practical purpose, in this article hyperglycemia is defined as any BG value > 140 mg/dl or > 7.8 mmol/L (note. 1 mmol/L = 18 mg/dl glucose) ⁽⁴⁾

Pathophysiology

The basic mechanism of stress hyperglycemia in acute stroke is similar to other acute illness or injury, ie increase in the concentration of counterregulatory hormones and cytokines⁽³⁾. Epinephrine mediates stress

hyperglycemia by altering postreceptor signaling, resulting in insulin resistance. Epinephrine also increases gluconeogenesis and suppresses insulin secretion. In addition to hyperglycemia, another effect of epinephrine is hypokalemia (via intracellular shift). Glucagon increases gluconeogenesis and hepatic glycogenolysis. Glucocorticoids and various cytokines also considerably contribute to stress hyperglycemia.

Epinephrine	skeletal muscle insulin resistance via altered postreceptor signaling
	increased gluconeogenesis
	increased skeletal muscle and hepatic glycogenolysis
	increased lipolysis; increased free fatty acids
	direct suppression of insulin secretion
Glucagon	increased gluconeogenesis
	increased hepatic glycogenolysis
Glucocorticoids	skeletal muscle insulin resistance
	increased lipolysis
	increased gluconeogenesis
Growth hormone	skeletal muscle insulin resistance
	increased lipolysis
	increased gluconeogenesis
Norepinephrine	increased lipolysis
	increased gluconeogenesis; marked hyperglycemia only at high concentrations
Tumor necrosis factor	skeletal muscle insulin resistance via altered postreceptor signaling
	hepatic insulin resistance

Why does glucose, the main energy substrate for the brain, cause damage of brain tissue at the time of cerebral ischemia ?

Shortly after being deprived of oxygen, metabolism within penumbral tissue changes from aerobic to anaerobic glycolysis which is less energy efficient and produces lactate and unbuffered hydrogen ions. Experimental models have consistently shown that animals made hyperglycemic before induction of ischemia have higher levels of lactate than euglycemic controls. Hyperglycemia may initially be neuroprotective,

with increased glucose available for metabolism and ATP production. Persisting anaerobic metabolism results in the development of intracellular acidosis. It has been shown using both pH-sensitive microelectrodes and ^{31}P nuclear magnetic resonance spectroscopy that the brain pH of animals pretreated with glucose is considerably more acidotic than saline treated controls. Acidosis may exacerbate penumbral injury through enhancement of free radical formation, activation of pH dependent endonucleases, and glutamate release with subsequent alteration of intracellular Ca^{++} regulation and mitochondrial failure.

There is currently no direct proof that lactate is detrimental to the ischemic brain. In vitro work using murine hippocampal slices has shown that glucose and acidosis are detrimental to cells whereas lactate is not. Using PET scanning it has been shown that lactate may be the preferred energy supply to the brain especially during times of stress. This is relevant to the management of hyperglycemia in acute ischemic stroke patients. If the ischemic brain is dependent on lactate for its source of energy, targeted euglycemia may result in less glucose load to the brain and thus less substrate for anaerobic metabolism, therefore attenuated lactate production. ⁽⁵⁾

Summary of Evidence Supporting a Detrimental Role for Elevated Glucose in Stroke ^(3,5,6)

1. Experimental ischemic damage is worsened by hyperglycemia.
2. Experimental ischemic damage is reduced by glucose reduction.
3. Early hyperglycemia is associated with clinical infarct progression in brain imaging.
4. Early hyperglycemia is associated with hemorrhagic conversion in stroke.
5. Early hyperglycemia is associated with poor clinical outcome.

6. Early hyperglycemia may reduce the benefit from recanalization.
7. Immediate insulin therapy reported beneficial in acute myocardial infarction and surgical critical illness.

So what?

There is strong rationale to treat stress hyperglycemia in acute stroke. Should we extrapolate the results of randomized clinical trials on glucose control in critically ill patients ?

Randomized clinical trials on glucose control in critically ill patients were first reported in 1995. These studies were done at a time when physicians did not place a high priority on glucose control in hospitalized patients. Physicians used a sliding scale to calculate insulin doses (the true purpose of the sliding scale is not to control glucose but to provide a contingency plan for insulin dosing so that nurses could decide the dose without needing to call the physician, which the sliding scale does admirably). Patients in the ICU with blood glucose concentrations over 11.1 mmol/L (200 mg/dL) were common ⁽⁷⁾ The DIGAMI (Diabetes Insulin-Glucose in Acute Myocardial Infarction) study was the first clinical trial of tight glucose control in the hospital. This randomized study compared intravenous insulin followed by multiple-dose insulin therapy versus standard care for patients with diabetes and acute myocardial infarction ⁽⁸⁾ . Although the authors did not define their protocol, attentive control of blood glucose from the time of admission to the postdischarge period reduced mortality at 1 year by 26%. In 2001, a Belgian group performed the first large randomized trial of tight glucose control in critically ill patients in a surgical intensive care unit. Most patients were recovering from coronary artery bypass surgery ⁽⁹⁾ . The authors enrolled anyone with elevated glucose concentrations, not just patients with diabetes. Tight control dramatically reduced the mortality rate from 8% in the control group (in which the glucose control

target was 10.0 mmol/L [<180 mg/dL]) to 4.6% in the normal glucose-control group (in which the glucose control target was 6.1 mmol/L [<110 mg/L]). Of note, the glucose control targets for all patients—diabetic or nondiabetic—were those typically set for nondiabetic patients. Although most diabetologists believed that tight glucose control would help, they were surprised by magnitude of the benefit. At that point, the pendulum was at its apogee on the side of tight glucose control, and major organizations issued guidelines endorsing tight glucose control in the ICU.

However, when the Belgian group applied their glucose-control protocol to medical ICU patients, the results were very different. The mortality rate in the tight control group was lower in patients who stayed in the ICU for 3 or more days but higher in those who stayed in the ICU less than 3 days⁽¹⁰⁾. Furthermore, the benefit was much smaller than that seen in the Belgian group's study of patients in the surgical ICU: a 6% reduction in mortality in patients with longer stays in the ICU rather than the 42% reduction seen in the surgical ICU. However In subsequent studies, including the NICE-SUGAR (the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation)—strongly discouraged against tight glucose control.⁽¹¹⁾

Past and Present Attitude

In 2004 active lowering of elevated blood glucose by rapidly acting insulin is recommended in most published guidelines, even in nondiabetic patients (European Stroke Initiative [EUSI] guidelines >10 mmol/L, American Stroke Association [ASA] guidelines >300 mg/dL)⁽⁶⁾ However, current evidence indicates that persistent hyperglycemia (>140 mg/dl) during the first 24 hours after stroke is associated with poor outcomes, and thus it is generally agreed that hyperglycemia should be treated in patients with acute ischemic stroke. The minimum threshold describe in previous statements likely was too

high. Therefore a lower serum glucose concentration (possible >140 to 185 mg/dl) should trigger administration of insulin (Class Iia, Level of Evidence C)
(12)

Conclusion

Stress hyperglycemia is common after acute stroke and may be caused by the increased release of counterregulatory hormones, such as epinephrine, glucagon and glucocorticoid.

Current recommendation should be followed regarding the treatment of stress hyperglycemia in patient with acute stroke, in view of the grievous consequences to short-term mortality and poor functional recovery.

Very good understanding in handling stroke hyperglycemia is important before considering the administration of parenteral maintenance fluid therapy containing glucose, in order to ensure functional recovery and avoid complications.

References

1. J. Broderick, S. Connolly, E. Feldmann, D. Hanley, C. Kase, D. Krieger, M. Mayberg, L. Morgenstern, C. S. Ogilvy, P. Vespa, et al. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage in Adults: 2007. *Stroke*, June 1, 2007; 38(6): 2001 – 2023
2. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke*. 2001
3. Kelly S Lewis, Sandra L Kane-Gill, Mary Beth Bobek, and Joseph F Dasta Intensive Insulin Therapy for Critically Ill Patients *Ann. Pharmacother.*, Jul 2004; 38: 1243 - 1251.
4. Etie S. Moghissi, Mary T. Korytkowski, Monica DiNardo, Daniel Einhorn, Richard Hellman, Irl B. Hirsch, Silvio E. Inzucchi, Faramarz Ismail-Beigi, M. Sue Kirkman, and Guillermo E. Umpierrez. American Association of Clinical

Endocrinologists and American Diabetes Association Consensus Statement on Inpatient Glycemic Control Diabetes Care June 2009 32:1119-1131

5. M. T. McCormick, K. W. Muir, C. S. Gray, and M. R. Walters. Management of Hyperglycemia in Acute Stroke: How, When, and for Whom? Stroke, July 1, 2008; 39(7): 2177 – 2185
6. Lindsberg PJ and Roine RA. Hyperglycemia in Acute Stroke. Stroke 2004;35:363-364
7. Comi, R. J. (2009). Glucose Control in the Intensive Care Unit: A Roller Coaster Ride or a Swinging Pendulum?. ANN INTERN MED 150: 809-811
8. Malmberg K, Rydén L, Efendic S, Herlitz J, Nicol P, Waldenström A; et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. J Am Coll Cardiol. 1995;26:57-65. [PMID: 7797776]
9. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M; et al. Intensive insulin therapy in the critically ill patients. N Engl J Med. 2001;345:1359-67.
10. van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I; et al. Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;354:449-61
11. The NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360:1283-1297
12. H. P. Adams Jr, G. del Zoppo, M. J. Alberts, D. L. Bhatt, L. Brass, A. Furlan, R. L. Grubb, R. T. Higashida, E. C. Jauch, C. Kidwell, et al. Guidelines for the Early Management of Adults With Ischemic Stroke: A Guideline From the American Heart Association/ American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Stroke, May 1, 2007; 38(5): 1655 – 1711

NEW PARADIGM IN MAINTENANCE FLUID THERAPY FOR OBSTETRIC PATIENTS

Iyan Darmawan

Introduction

Within the context of fluid therapy, obstetric patients can be considered special populations because profound changes in cardiovascular physiology that occur during pregnancy are accompanied by unique changes in sodium, water and electrolyte metabolism. Therefore, a basic understanding of these changes is important in administering parenteral fluid during pregnancy. Two aspects of maintenance fluid therapy in obstetric patients will be discussed :nonoperative and postoperative.

Normal Changes During Pregnancy ⁽¹⁾

Fluid, Electrolyte and Acid-Base Changes during Normal Pregnancy consist of:

- Plasma Hypo osmolarity (~ less 10 mOsm/L)
- Hyponatremia despite cumulative retention of 500-900 mEq Na⁺
- Decreased plasma serum Ca and Mg
- Respiratory alkalosis (may be worsened by severe vomiting)
- Decreased BUN and creatinine
- Decreased serum protein concentration

Hemodynamic changes during normal pregnancy have been characterized as:

- Increased cardiac output
- Decreased Blood Pressure
- Decreased Peripheral Vascular Resistance
- Increased Plasma volume
- Increased Renal blood flow
- Increased GFR

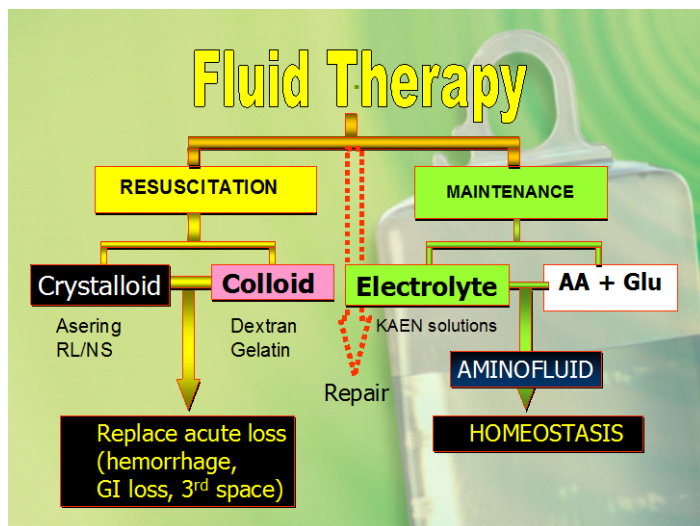
- Renin-Angiotensin-Aldosterone system greatly stimulated

In general, there is retention of water and electrolytes, despite the serum levels of important electrolytes may be low because of plasma volume expansion. ⁽¹⁾

Classification of fluid therapy.

Fluid therapy can be simply divided into 3 types, determined by each goal, rate of administration and type of infusion solutions, such as:

1. Resuscitation fluid therapy
2. Maintenance fluid therapy
3. Repair fluid therapy



In resuscitation fluid therapy, the primary objective is to replace acute extracellular fluid loss, such as occurring in acute dehydration, hemorrhage and intraoperative. Thus, it preserves tissue perfusion and oxygen delivery. For this purpose, isotonic fluids such as acetated ringer's

(Asering), lactated ringer's and Normal saline are used, based on the associated acid-base disturbance. For example, in acute diarrhea where acidosis ensues, acetated ringer's or lactated ringer's are more appropriate because they have bicarbonate buffers to combat acidosis. On the other hand, during severe vomiting when there are severe depletion of chloride ion and alkalosis, normal saline is better as starting solution because it contains higher content of chloride than the former.

Postpartum hemorrhage is a typical indication of resuscitation fluid therapy in obstetric patients. In addition, isotonic fluids such as acetated ringer's, lactated ringer's and colloid are used as intraoperative solutions.

Repair fluid therapy is aimed at correcting extreme electrolyte or acid-base abnormalities, such as severe hypokalemia, life-threatening hyponatremia and acidosis/alkalosis.

Maintenance fluid therapy is given to patients whose hemodynamics are not compromised by shock or hypotension. It replaces normal daily fluid and electrolyte excretion and in patients who do not have adequate oral fluid or nutrition intake. Normally, the maintenance infusion solutions contain sodium and potassium in accordance with normal daily requirement with a certain concentration of carbohydrate. Today's maintenance solution is represented by Aminofluid which contains electrolytes, microminerals, zinc, as well as 3% Aminoacid and 7.5% anhydrous glucose, in dual chamber bag.

Table 1. Composition of Aminofluid

Composition	Aminofluid®	Daily requirement ⁽³⁾
Water	2000	30-40 ml/kg/day
Na ⁺	70	1-2 mEq/kg/day
K ⁺	40	1-2 mEq/kg*/day
Cl ⁻	70	As needed
Mg ⁺⁺	10	8-20 mEq/day

Ca ⁺⁺	10	10-15 mEq/day
P	20	20-40 mEq/day
Zn	10 µmol	
Amino acid	AA 60 g	0.8 g/kg/day [‡]
Glucose	150 g ¥	

* K⁺ requirement for homeostasis 20-30 mEq/day⁽²⁾; ‡ Amino acid requirement in nonstressed patient; ¥ protein-sparing effect. Zinc content to replace daily urinary excretion of 7.6 µmol

RATIONALE FOR MAINTENANCE FLUID THERAPY

There are various reasons that the following situation are unraveled to attending physicians:

- Majority of pregnant patients are already in moderate dehydration, but their hemodynamics are not severely compromised. Some patients may already have had insufficient oral fluid intake before hospitalization or fever which cause increased insensible water loss.
- Anxiety, depression or fear.
- Malaise or fatigue may be the reason why the relatives bring the patient to hospital.
- Unfamiliarity or dislike of hospital food
- Insufficient oral intake (too weak to chew or bitter dry tongue)
- Inflexible mealtimes
- Anorexia, nausea, or distress
- Suppressed level of consciousness.

Such information may be overlooked, while doctors pay more attention in selecting the right medications for patient's condition, and at the same time ignore patients' need of maintenance support.

Goal of maintenance fluid therapy can be summarized as follows:

1. Fulfills daily physiological requirements for homeostasis. Restore quickly the depleted fluid and electrolyte content of intracellular compartment
2. Prevents electrolyte & acid base disorders

3. Supports primary therapy of patients' illness
4. Enzymatic process & protein synthesis
5. Facilitates recovery

What are the features of a good maintenance solution?

- Practical, easy and safe to administer
- In addition to basic electrolytes (Na^+ , K^+ , Cl^-) also contains microminerals (Mg^{++} , Ca^{++} , P) which are required for cellular metabolism
- The presence of value added zinc helps to promote tissue healing
- Contains high quality amino acids (BCAA enriched, high in EAA) to promote protein synthesis
- Glucose to maintain euglycemia, prevent ketosis, and protein-sparing effects.

One of possible candidates to fulfill the above criteria is Aminofluid®.

Why are microminerals also necessary?

In addition to basic minerals, such as sodium, potassium, chloride, today's maintenance solution should contain microminerals which are required for cellular metabolism. The role and recommended dosage are given in following table 2:

Table 2. Functions and recommended daily intake of water, electrolytes

	Functions ⁽³⁾	ASPEN* ⁽³⁾	Aminofluid
Water(ml)	Essential component of cells and other fluid compartments, temperature regulation, solvent, lubricant	30-40 ml/kg	2000
Na^+ (mEq)	In combination with chloride to maintain blood volume and	1-2 mEq/kg	70

	osmolarity, regulate charging potential in neuromuscular junction, and influence acid-base balance		
K^+ (mEq)	Neuromuscular excitability, protein and collagen synthesis, enzymatic process in cellular energy production. In combination with sodium and calcium also maintains normal heart rhythm. Part of body's buffer system	1-2 mEq/kg	40
Cl^- (mEq)	Along with sodium maintains osmolarity of ECF. Maintain fluid balance. Maintain acid-base balance. Exchange of oxygen and carbodioxide in red blood cells. Component of gastric juice	as needed to maintain acid-base balance	70
Mg^{++} (mEq)	Extremely important for enzyme systems. Neuromuscular activities. Essential for proper metabolism of ATP, Na^+-K^+ pump. Facilitate neuromuscular integration and stimulate secretion of parathyroid hormone. Cardiac function.	8-20	10
Ca^{++} (mEq)	Proper development of bones and teeth, neuromuscular function, blood clotting ability, acid-base balance, and activation of certain enzymes	10-15	10
P(mmol)	essential for metabolism of nutrients such as carbohydrate, lipids and protein. Co-factor in numerous enzyme systems of cellular metabolism. ATP. Crucial component of DNA. Formation of bones. Acid-base regulation.	20-40	20

Zinc is one of essential trace elements provided in today's maintenance solution

	Functions	Urinary excretion	Aminofluid
Zinc	Promote wound healing. Zinc is necessary for the formation of collagen, which is essential material for tissue healing and repair. Zinc also provides immunity against disease.	7.6 micromol/day	10 micromol/L

	Required for metabolism of nutrients such as carbohydrates, protein, fat, and synthesis of nucleic acids (DNA and RNA)		
--	--	--	--

There is also evidence that zinc supplementation could offer benefit to pregnant women and their babies. One study showed that prenatal zinc supplementation can increase birth weight, and another indicated reduced incidence of diarrhea and other morbidities in the infants⁽⁴⁾

Why should we provide BCAA (branched-chain amino acids) in maintenance solution?

Leucine, isoleucine and valine are three amino acids most frequently studied and proven to have some pharmacological effects ^(5,6,7,8,9):

- Important precursors in the synthesis of glutamine and alanine in skeletal muscle
- Increased consumption of BCAA occurs in many illnesses
- Leucine positively affects protein synthesis in experimental model of sepsis and burns
- BCAA improves appetite by competitively block the entry of tryptophan, precursor of serotonin, into central serotonergic nervous system. Therefore, the decrease in serotonin level will reduce the stimulation of melanocortin system in the hypothalamus, followed by improved appetite
- In septic encephalopathies BCAA : AAA ratio decreases
- Patients surviving sepsis had higher concentrations of the branched chain amino acids
- BCAA promotes cerebral blood flow

Typical Patients requiring maintenance fluid therapy (non-operative phase)

Hyperemesis Gravidarum

The following electrolyte disorders and abnormal glucose levels can occur in patients with hyperemesis gravidarum:

- Hyponatremia
- Hypochloremia
- Alkalosis (severe vomiting) or ketosis (anorexia, insufficient intake of carbohydrate)
- Hypoglycemia/Hyperglycemia DM (?)
- Hypokalemia

The approach to patients with hyperemesis gravidarum should include:

- What is the hemodynamic status? In the presence of shock or hypotension give isotonic fluids at 20 ml/kg/hr; if shock is absent 3 ml/kg/hr. The amount of fluids to be adjusted to the severity of dehydration and if the patients are expected to immediate recovery to oral intake (eg, 1.5-3 L per day)
- Are electrolytes (Na^+ , K^+ , Cl^-) and blood gas (acid-base) checked?
- Is albumin measured? (hypoalbuminemia tends to cause alkalosis)
- If not, can acidosis or alkalosis detected by clinical examination? (respiratory rate, breath smell?). In some patients ketosis (acidosis) may co-exist with hypochloremic alkalosis.
- Is blood glucose checked? (diabetic patients tend to have ketoacidosis)
- Types of infusion solutions depend on electrolyte, blood gas and glycemia can may change from time to time

In general, average patients with hyperemesis gravidarum may be given initially 0.9 % NaCl –in D5W (or Ringer D5) 500-1000 ml, followed by maintenance fluid. New generation maintenance solution, Aminofluid® is already available as a better alternative.

Preeclampsia/Eclampsia

In fact, in patients with pre-eclampsia or eclampsia the type of fluid therapy is for maintenance, because patients are not in shock. Plasma volume is reduced in women with pre-eclampsia (pregnancy induced complication that includes high blood pressure). It is possible that women with pre-eclampsia might benefit from expanded plasma volume if it were to increase blood circulation for the mother and baby. However, the review of trials found there was not enough evidence to show the effects of plasma volume expansion for women with pre-eclampsia. Fluid restriction is advisable to reduce the risk of fluid overload in the intrapartum and postpartum periods. In usual circumstances, total fluids should be limited to 80 ml/hour or 1 ml/kg/hour. Fluid therapy should be limited to maintenance crystalloid (11,12,13)

New findings have reported that the higher osmolarity of electrolyte infusion the longer the water retention. For example, water retention by the body is longer after normal saline than lactated ringer's or acetated ringer's, where as water is excreted fastest after 5% dextrose.⁽¹⁴⁾

Over the last 20 years, pulmonary edema has been a significant cause of maternal death. This has often been associated with inappropriate fluid management. There is no evidence of the benefit of fluid expansion and a fluid restriction regimen is associated with good maternal outcome. There is no evidence that maintenance of a specific urine output is important to prevent renal failure, which is rare. The regime of fluid restriction should be maintained until there is a postpartum diuresis, as

oliguria is common with severe pre-eclampsia. If there is associated maternal haemorrhage, fluid balance is more difficult and fluid restriction is inappropriate ⁽¹⁵⁾

Postoperative Maintenance Fluid Therapy

Before giving maintenance fluid and nutrition therapy during postoperative period, the following should be considered:

- Fatal pulmonary oedema may occur 36 hours postoperatively if parenteral fluid retention exceeds 67 ml/kg/d; postoperative fluid intake should be limited to < 2000 ml/day ⁽¹⁵⁾
- Recovery of GI function is faster in patients receiving ≤ 2 L; 77 mEq Na^+ compared to > 3 L; 154 mEq Na^+ , postoperatively. Current recommendation of postoperative $\text{Na}^+ < 60$ -100 mEq ⁽¹⁶⁾
- Hypoalbuminemic surgical patients already have interstitial expansion. This can be aggravated by administration of high sodium parenteral fluid, causing delayed recovery of surgical wound ⁽¹⁷⁾
- 1. Water and sodium excretion is more slowly in postoperative patients receiving high sodium parenteral fluid ⁽¹⁴⁾
- Protein-sparing effect of carbohydrate solution is 600 kcal. ⁽¹⁸⁾

In line with innovation of technology in various fields, novel maintenance solution AMINOFLUID has been introduced. It contains electrolytes, microminerals and zinc, 3% amino acids (9 g BCAA) and 7.5% glucose. One dual chamber 1000 ml soft bag of Aminofluid provides 300 kcal. It may be better alternative for postoperative maintenance in straightforward surgery

(e.g Ovarian cystectomy, Laparoscopic surgery, caesarean section). as well as early postoperative support in complicated major surgery. One to two 1000 ml dual-chamber soft bags per day can be administered based on fluid requirement

Conclusion:

Obstetric patients pose a special problem in fluid therapy. Knowledge of underlying conditions necessitating fluid therapy is essential in order to give proper and rational treatment.

Fluid therapy should be directed based on the hemodynamic, dehydration status, electrolyte and acid-base status. Hydration status of postoperative obstetric patients should be evaluated and treated accordingly to ensure rapid recovery and prevent complications.

References:

1. Paller M.S. Ferris T.F. Fluid and Electrolyte Disorders of Pregnancy. In Koko & Tannen Fluids and Electrolyte 3rd ed. WB Saunders Co. p806
2. Tannen RL. Potassium Disorders. In Kokko & Tannen : Fluids and Electrolytes. 3rd Edition WB Saunders 1996. p 114
3. ASPEN Board of Directors and the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. JPEN Vol 26, No1 Suppl Jan-Feb 2002.
4. Abi Berger Science commentary: What does zinc do? BMJ 2002; 325: 1062
5. Alessandro Laviano; Michael M Meguid; Akio Inui; Maurizio Muscaritoli; Filippo Rossi-Fanelli. Therapy Insight: Cancer Anorexia-Cachexia Syndrome-When All You Can Eat Is Yourself. Nat Clin Pract Oncol. 2005;2(3):158-165.
6. Rossi-Fanelli et al. Branched Chain Amino Acids: The best compromise to achieve anabolism. Curr Opin Clin Nutr Metab Care 8:408-414. 2005 Lippincott Williams & Wilkins.

7. Jean-Pascal De Bandt and Luc Cynober Therapeutic Use of Branched-Chain Amino Acids in Burn, Trauma, and Sepsis. *J. Nutr.* 2006 136: 308S-313S
8. Samuel N. Cheuvront, Robert Carter, III, Margaret A. Kolka, Harris R. Lieberman, Mark D. Kellogg, and Michael N. Sawka. Branched-chain amino acid supplementation and human performance when hypohydrated in the heat *J Appl Physiol*, Oct 2004; 97: 1275 - 1282.
9. Calder PC. Branched-chain amino acids and immunity. *J Nutr.* 2006 Jan;136(1 Suppl)
10. E. Blomstrand A Role for Branched-Chain Amino Acids in Reducing Central Fatigue *J. Nutr.*, February 1, 2006; 136(2): 544S - 547S
11. Duley L, Williams J, Henderson-Smart DJ Plasma volume expansion for treatment of pre-eclampsia. *Cochrane Database of Systematic Reviews* 2007 Issue 1
12. Royal College of obstetricians and Gynaecologists. Guidelines: management of Eclampsia. <http://www.rcog.org.uk>. Valid until November 1999. Tuffnell DJ, Shennan AH, Waugh JJ, Walker JJ. The management of severe pre-eclampsia/eclampsia. London (UK): Royal College of Obstetricians and Gynaecologists; 2006 Mar. 11 p
13. REID F, LOBO DN, WILLIAMS RN, ROWLANDS BJ, Simon P.A (Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study *Clinical Science* (2003) **104**, (17–24) (Printed in Great Britain)
14. Arieff Allen L. Fatal Postoperative Pulmonary Edema. Pathogenesis & Literature Review. *CHEST* 1999;115:1371-1377
15. Lobo DN et al. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection. *Lancet* 2002 May 25.359(5320):1792-3
16. Hill G.L. Disorders of nutrition and metabolism in clinical surgery. Churchill Livingstone 1990
17. Schricker T. The catabolic response to surgery: how can it be modified by the anesthesiologist? *Canadian Journal of Anesthesia* 48:R13 (2001)

UPDATE ON CLINICAL USE OF MAGNESIUM IN OBSTETRICS

Iyan Darmawan

Introduction

Magnesium sulphate is the agent of choice for the prevention of eclamptic convulsions, but it is not clear if all pre-eclamptic patients should be given. Although magnesium is safe, it is not entirely without risk, particularly in areas where monitoring may be limited, and clinicians must consider the benefit/risk ratio of using the agent against the exposure of a large number of patients to a therapy which most of them do not need. There are also risks attached to using an unfamiliar form of treatment in areas where severe pre-eclampsia is infrequent¹. Most adverse effects are mild, but overdose may lead to respiratory embarrassment and even death if not carefully managed.

The mechanism of action of MgSO_4 ²

How MgSO_4 works is not completely understood. It is thought to cause cerebrovascular dilatation thus reducing cerebral ischemia. There is possibility that magnesium blocks calcium receptors by inhibiting N-methyl-D-aspartate receptors in the brain. Magnesium also produces a peripheral (predominantly arteriolar) vasodilatation thus reducing the blood pressure.

It also acts competitively in blocking the entry of calcium into synaptic endings thus modifying neuromuscular transmission. This transmission is affected by a predominantly presynaptic as well as a post-synaptic effect. The presynaptic release of acetylcholine is also reduced thus altering neuromuscular transmission. The precise mechanism of action for the tocolytic effects of MgSO_4 is not clearly defined but may be related to the action of magnesium as a calcium blocker thus inhibiting muscle contractions.

Is low level of serum ionized magnesium responsible for eclampsia?

To prove this causal relationship, Akhther and Rashid³ studied that serum levels of magnesium in fifty eclamptic patients before giving MgSO_4 was 0.47(0.15-1.04) mmol /L and 24 hours after giving the loading dose of MgSO_4 was 0.74(0.20- 2.0) mmol/ L. After MgSO_4 infusion, level raises. This change is significant ($P < .001$). Change in ionized magnesium level was followed by change in diastolic blood pressure, systolic blood pressure, mean arterial pressure and albuminuria. These changes are also significant ($p < .001$)

Magnesium sulphate indirectly prevents stroke

Preeclampsia, which is characterized by the new onset of hypertension and proteinuria during the pregnancy, affects 3–5% of pregnancies worldwide and the proportion of preeclampsia or eclampsia in pregnancy-related strokes is between 25 and 45%⁴

For acute treatment of preeclampsia and eclampsia, magnesium sulfate therapy was superior to phenytoin in controlling eclamptic seizures, and a loading dose of magnesium sulfate significantly improved cerebral perfusion.^{4,5}

MgSO_4 Regimens⁵

There are principally two main regimens available for the administration of MgSO_4 .

- Pritchard Regimen, the loading bolus dose of 4 g of MgSO_4 is given slowly intravenously over 5-10 min and this is followed by 10 g given intramuscularly (5 g in each buttock). Subsequently, 5 g is given intramuscularly into alternate buttocks every 4 h.
- Zuspan regimen, the loading dose consists of an initial intravenous dose of 4 g slowly over 5-10 min

followed by a maintenance dose of 1-2 g every hour given by an infusion pump.. Whatever regimen chosen, the drug should be administered till 24 h after delivery or after the last fit (whichever comes last).

Dosage and administration

There are several dosage regimes for the use of magnesium in pre-eclampsia, largely dependent on the availability of sophisticated delivery and monitoring systems. The main risk of magnesium infusion is accidental massive overdose with neuromuscular blockade and respiratory failure. Intravenous magnesium should be delivered using a syringe driver, rather than the far more risky approach of an infusion through a drip set. Where such facilities are not available, the intramuscular route is reasonably well tolerated and far less likely to produce dangerously high concentrations of plasma magnesium.

Some suggested approaches to magnesium dosing are given in Table.

Table Recommended MgSO₄ dosage regimes. Maintenance should be continued for 24 hours after delivery or the last convulsion.¹

Indication	Route	Loading Dose	Maintenance
Preeclampsia/ eclampsia	IV	4–6 g intravenously over 15–20 min	1–2 g hr ⁻¹ infusion
	IM	5 g (10 mL) 50% MgSO ₄ into each buttock	5 g im every 4 hours
	Combined	4–6 g intravenously over 15–20 min	5 g im every 4 hours

Indication	Route	Loading Dose	Maintenance
Tocolysis	IV	6 g intravenously over 15–20 min	2–5 g hr ⁻¹ infusion

Tocolysis

A meta-analysis of tocolytics showed that all agents were more effective than placebo at delaying labour at 48 h and at 7 days, but there were no other significant differences. This analysis suggested that prostaglandin inhibitors provided the best combination of tolerance and delayed delivery. Magnesium achieved a success rate of 82% at delaying labour by 48 h, superior to all other agents other than the prostaglandin inhibitors but was less effective at 7 days. Part of the difficulty in comparing the controversial evidence may lie in the variety of dosage regimes employed. Lewis pointed out that dosage was crucial with low-dose regimens (4 g loading dose and 2 g h⁻¹ infusion) achieving less than 75% efficacy, while a higher dose (6 g loading dose and >2 g h⁻¹) achieved over 85% efficacy. Elliott *et al.* suggested a dosage regimen for MgSO₄ of a 6-g loading dose followed by an infusion of 3–5 g h⁻¹. There seem, therefore, arguments both for and against the use of magnesium for tocolysis, and the clinical choice should probably be influenced by drug availability and familiarity until such time as convincing evidence of efficacy and safety for the various agents is available. Where high-dose magnesium is to be used, it appears important that adequate plasma levels are obtained, and this should be one area where therapy is guided by measurements of plasma Mg²⁺ concentration with a lower limit of 2.5 mmol l⁻¹ and an upper limit of 4 mmol l⁻¹ probably being advisable, but there are no studies to confirm these ranges. Magnesium sulphate and nifedipine remain the most widely used first-line agents for tocolysis in the United States at present ^{1,6}

Tocolysis and Intraventricular Hemorrhage (IVH) in preterm infants

Petrova and Mehta ⁶ studied eighty-nine IVH cases and 89 controls who were comparable for parity, mode of delivery, antenatal corticosteroid exposure, and surfactant administration

Among the IVH cases, 30.3% of infants were exposed to tocolytic MgSO_4 as compared to 47.2% of controls (Odds Ratio adjusted 0.471, 95% Confidence Interval 0.241, 0.906). They concluded that among the preterm born infants with gestational age 23–31 wks and IVH, tocolytic MgSO_4 exposure was less likely to be observed than in neonates with similar clinical characteristics but without IVH, thereby suggesting that antenatal exposure to MgSO_4 may have a protective effect against IVH.

References:

1. James M.F.M . Magnesium in obstetrics. Best Practice & Research Clinical Obstetrics & Gynaecology Volume 24, Issue 3, June 2010, Pages 327-337
2. Tukur J, The use of magnesium sulphate for the treatment of severe pre-eclampsia and eclampsia Annals of African Medicine. Sokoto: Jun 2009. Vol. 8, Iss. 2; p. 76
3. Akther R, Rashid M. Is Low Level of Serum Ionized Magnesium Responsible for Eclampsia?. Journal of Bangladesh College of Physicians & Surgeons. Dhaka: 2009. Vol. 27, Iss. 2; p. 76
4. Tang SC, Jeng SJ. Management of stroke in pregnancy and the puerperium. Expert Review of Neurotherapeutics. London: Feb 2010. Vol. 10, Iss. 2; p. 205
5. Bhattacharjee N, Saha SP, Ganguly RP, Patra KK. A randomised comparative study between low-dose intravenous magnesium sulphate and standard intramuscular regimen for treatment of eclampsia. Journal of Obstetrics and Gynaecology Bristol: May 2011 Vol. 31, Iss. 4; pg. 298
6. Petrova A and Mehta R Magnesium Sulfate Tocolysis and Intraventricular Hemorrhage in Very Preterm Infants Indian Journal of Pediatrics, 2012, Volume 79, Number 1, Pages 43-47

FLUID BALANCE IN THE ELDERLY PATIENT

Iyan Darmawan

Fluid balance is of significant concern during hospitalization, particularly in older adult and very young children. Fluid intake may not meet the body's demands, resulting in decreased saliva secretions, decreased absorption of vitamin B₁₂, decreased secretion of intrinsic factors, decreased peristalsis, increased constipation and diverticulosis.⁽¹⁾ Most developed world countries have accepted the chronological age of 65 years as a definition of 'elderly' or older person.

The changes that occur in organs that regulate fluid balance are also important consideration in the evaluation of the fluid status in the older adult..⁽²⁾ For instance, the genitourinary system in the older adult shows a decrease in the number of nephrons, a marked decrease in blood flow, and a decreased ability to respond to stress that result from increased body needs in dehydration or fluid overload. Renal changes result in the kidney's reduced ability to concentrate and dilute urine in response to water and salty excess and to metabolize and excrete drugs.⁽³⁾ It is also known that elderly individuals lack thirst response to increased hyperosmolarity in dehydration because of decreased sensitivity of chemoreceptor and osmoreceptor in the wall of blood vessels. The elderly have a delayed and less intense thirst response than do younger persons.

The older body tends to secrete ADH despite decreased blood tonicity (the syndrome of inappropriate ADH secretion [SIADH]), especially in a person with chronic cardiac, hepatic, or renal disease. Increased ADH concentration and secretion increase the risk of hyponatremia most intensely when fluid intake increases--a situation common with IV hydration during hospitalization or surgery.⁽⁴⁾ Combine these factors and reduced cardiac efficiency and decreased blood flow to

the organs, render older adults to higher risk of fluid imbalance.

Though it is not known why nocturia increases with old age, it has been suggested that GFR and clearance of electrolytes decreases with standing and is enhanced with horizontal positioning.⁽⁵⁾ Nocturia and urinary incontinence may cause the elderly to voluntarily restrict their fluid intake. Holding fluids 2 hours before bedtime may help decrease the frequency of nocturia and nighttime incontinence.⁽⁶⁾

The nurse must take all of these factors into account when preparing to initiate IV therapies in the older adult. For instance, IV rehydration must be performed with caution in the older adult because of the inability of this population to excrete fluid as rapidly as do younger patients. In addition, careful administration of salt-containing fluid is required for the volume depleted older adult. If an excess of sodium is ingested, resulting in fluid overload, the kidney is less able to compensate because of age-related changes.

Resuscitation fluid therapy

Elderly patients arriving in the emergency unit with hemodynamic instability or hypovolemic shock often pose the emergency staff in dilemmatic situation. Should aggressive rehydration be initiated, the risk of cardiac overload is overwhelming. On the other hand, inadequate fluid resuscitation may not achieve the resuscitation endpoint of MAP (mean arterial pressure) 70 mmHg. Furthermore, if the MAP has not reached 60 mmHg after 24 hours, patients will end up in acute renal failure.

Maintenance fluid therapy

In nonsurgical patients average fluid balance can be estimated as follows:

Water gain		Water Loss	
Sensible Drink Food	1200 ml 1000 ml	Sensible Urine Feces Sweat	1500 ml 100 ml 50 ml
Insensible Oxidative metabolism	350 ml	Insensible Lungs Skin	400 ml 500 ml
TOTAL	2550 ml	Total	2550 ml

Thus, the daily fluid requirement can be estimated by measuring urine output added to predicted IWL (insensible water loss). The amount and colour of urine may reflect the hydration status. Patients with dementia or altered sensoria are at the highest risk for dehydration and hypernatremia secondary to decreased fluid intake.

Adequate hydration is estimated at 1500 to 2500 mL per day in the absence of contraindicating conditions such as heart failure. If older patient needs an intravenous fluid, recommended infusion solution is maintenance solution which contain moderate sodium and enough potassium, such as KAEN3B, KAEN 3A, and KAEN MG3. When, fatigue and anorexia predominate, AMINOFLUID is the maintenance of choice.

Postoperative fluid balance

Unlike in nonsurgical setting, urine output is not a reliable indicator of hydration status because surgical stress induces the release of aldosterone and ADH which in turn cause fluid retention. Recent finding suggest that moderate postoperative maintenance fluid intake of 1500-2000 ml and low sodium (60-100 mEq) daily avoid fluid overload in postoperative patients.⁽⁷⁾ The low urine output should neither prompt surgeons to consider dehydration nor prescribe aggressive fluid administration.

Last but no least, the selection of vein is important in elderly patients because their veins tend to be more

“fragile” and prone to phlebitis. Forearm or antecubital veins should be selected for i.v. site when giving hypertonic fluid (such as peripheral parenteral nutrition products, injectable drug admixtures). Veins of dorsal vein should be avoided in such cases.

Reference:

1. Fabian Beth. Intravenous therapy in older adult . Terry Judy. Intravenous therapy. Clinical Principles and Practice.WB Saunders Company 1995. pp 495-498
2. Kristin Larson, Fluid Balance in the Elderly: Assessment and Intervention - Important Role in Community Health and Home Care Nursing Geriatr Nurs 24(5):306-309, 2003. © 2003 Mosby, Inc
3. Andrew E. Luckey, MD; Cyrus J. Parsa, MD Fluid and Electrolytes in the Age *Arch Surg.* 2003;138:1055-106
4. Mark H. Beers. The Merck Manual of Geriatrics 3rd edition. Chapter 57. Disorders of water and electrolyte balance.
5. Radke KJ. The aging kidney: structure, function, and nursing practice implications. ANNA J 1994;21:181-193.
6. O'Donnell ME. Assessing fluid and electrolyte balance in elders. Am J Nurs 1995;95:40-46.
7. Fiona REID, Dileep N. LOBO, Robert N. WILLIAMS, Brian J. ROWLAND Sand Simon P. ALLISON (Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study Clinical Science (2003) 104, (17–24)

ESAS (EDMONTON SYMPTOM ASSESSMENT SYSTEM)

Iyan Darmawan

ESAS was originally designed as a tool to assess most common symptoms in cancer patient: pain, tiredness, depression, anxiety, drowsiness, loss of appetite, wellbeing and shortness of breath. The severity at the time of assessment of each symptom is rated from 0 to 10 on a numerical scale. 0 means that the symptom is absent and 10 is the worst possible severity. The patient and family should be taught how to complete the scales. It is the patient's opinion of the severity of the symptoms that is the 'gold standard' for symptom assessment. For good symptom management, ESAS should be used as one part of a holistic clinical assessment. By doing ESAS you might be surprised that many hidden important complaints are revealed.^{1,2,3}

How to do the ESAS?

The patient circles the most appropriate number to indicate where the symptom is between the two extremes

No pain 0 1 2 3 4 5 6 7 8 9 10 Worst possible pain

The circled number is then transcribed onto the symptom assessment graph (see "ESAS graph" below). Synonyms for words that may be difficult for some patients to comprehend include the following:

Depression	blue or sad
Anxiety	nervousness or restlessness
Tiredness	decreased energy (but not necessarily sleepy)
Drowsiness	Sleepiness
Depression	blue or sad
Anxiety	nervousness or restlessness
Wellbeing	overall comfort, both physical and otherwise; truthfully answering the question. "How are you?"

Ideally, patients fill out their own ESAS. However, if the patient is cognitively impaired or for other reasons cannot independently do the ESAS, it can be completed with the assistance of a caregiver (eg family member, friend). If the patient cannot participate in the symptom assessment, or refuses to do so, the ESAS is completed by the caregiver alone. Note: when the ESAS is completed by the caregiver alone, the subjective symptom scales are not done (i.e tiredness, depression, anxiety, and well being) and the caregiver assesses the remaining symptoms as objectively as possible, i.e. pain assessed on the basis of a knowledge of pain behaviours, appetite is interpreted as the absence or presence of eating, nausea as the absence or presence of retching or vomiting, and shortness of breath as laboured or accelerated respirations that appears to be causing distress for the patient.

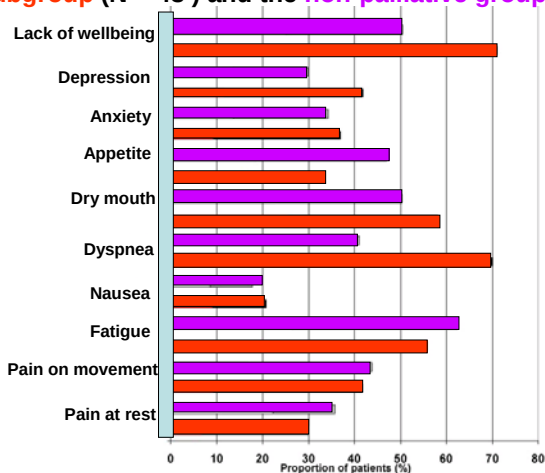
Can the ESAS be utilized for non-cancer patients?

Current report by Sigurdardottir and Haugen (2008)¹ showed that ESAS is useful to assess the prevalence and severity of symptoms in non-malignant patients.

Many patients with advanced, serious, non-malignant disease belong to the population generally seen on medical wards. ESAS was completed for 160 patients. 79 (35.6%) were defined as palliative and 43 of them completed ESAS. Patients were defined as "palliative" if they had an advanced, serious, chronic disease with limited life expectancy and symptom relief as the main goal of treatment. The patients in the palliative group were older than the rest, and reported more dyspnea (70%) and a greater lack of wellbeing (70%). Other symptoms reported by this group were dry mouth (58%), fatigue (56%), depression (41%), anxiety (37%), pain at rest (30%), and pain on movement (42%).

Following is the result of their study.

Prevalence of distressing symptoms in the palliative patient subgroup (N = 43) and the non-palliative group (N = 117)



Sigurdardottir and Haugen BMC Palliative Care 2008 7:16

Surprisingly, fatigue, dry mouth, depression and anxiety which are commonly unnoticed by clinicians are significant in both groups of patients. Dyspnea is related to COPD in this series.

As part of holistic management of patients in medical wards, it is time now to pay more attention on the benefits of supportive therapy. As mentioned in previous articles, novel maintenance fluid (such as Aminofluid) helps overcome these distressing symptoms.

Reference:

1. Sigurdardottir, KR Haugen DF Prevalence of distressing symptoms in hospitalised patients on medical wards: A cross-sectional study *BMC Palliative Care* 2008, **7**:16
2. Moro C, et al. Edmonton symptom assessment scale: Italian validation in two palliative care settings *Supportive Care in Cancer*, 2006, Volume 14, Number 1, Pages 30-37
3. Watanabe S, et al. The Edmonton symptom assessment system—what do patients think? *Supportive Care in Cancer*, 2009, Volume 17, Number 6, Pages 675-683

SUPPORTIVE THERAPY IN MOST HOSPITALIZED PATIENTS

Iyan Darmawan

Maintenance fluid therapy has recently been defined as provision of water, electrolytes, microminerals, and basal requirement of glucose and amino acids to hemodynamically-stable individuals ⁽¹⁾

Who benefits from parenteral nutrition (PN) has been the subject of much debate and 4 recent meta-analyses. Methods: We reviewed the 4 meta-analyses that examined the prospective, randomized, clinical trials (PRCT) that compared PN with no nutrition support (standard care) for design, study population, outcomes evaluated, and results. Results: Overall, a total of 113

PRCT were included in the 4 meta-analyses. Despite the differences in populations studied and outcomes evaluated, some similarities emerged: 1) PN does not affect mortality; 2) PN does not reduce complications in normally nourished patients; 3) in malnourished patients, PN demonstrated a trend for reduced infections and complication rates; and 4) PN reduced postoperative complications in patients having surgery for cancer of the esophagus or stomach. Conclusion: PN does not appear to be beneficial for most hospitalized patients.

Among those with malnutrition or with upper gastrointestinal cancer, benefits may exist. ⁽²⁾

The majority of hospitalized patients have sufficient adipose tissue stores and can tolerate 5–10 days of inadequate energy provision ⁽³⁾ Therefore, medical patients can be classified into three categories based on their rehydration requirement and adequacy of nutritional intake

Patients in Medical Wards

Dehydrated
Previously well-nourished
Good appetite



Fluid & basic
electrolyte
maintenance

Dehydrated
Previously well-nourished
Or slightly
undernourished
Metabolically Non-stressed
Anorexia
Fatigue



Complete
Electrolyte, 3% AA,
5-10% glucose
maintenance

Previously malnourished
Or undernourished or
Metabolically stressed
Hypoalbuminemia
Debilitated



Parenteral Nutrition :
10 % AA, High NPC
(glucose , lipid)

Goals of maintenance fluid therapy can be summarized as follows:

1. Maintain electrolyte homeostasis
2. Prevent worsening of nutritional state in times of insufficient oral food intake
3. Keep normal blood sugar level, and other serum biochemistry
4. Increase appetite by reducing central serotonin level
5. Combat fatigue
6. Facilitate enzymatic process and protein synthesis

Who benefit most from AMINOFLUID maintenance fluid therapy?

1. Febrile illnesses
2. Dehydrated and anorexic, dyspeptic patients
3. Gastrointestinal diseases, post resuscitation of severe diarrhea, colonoscopy, gastroparesis
4. Acute Infectious diseases

5. Early post operative maintenance
(straightforward surgery)
6. Hyperemesis gravidarum (after 0.9% NaCl)
7. Stroke (after metabolic and electrolyte correction)

In conclusion, provision of full calories and high concentration amino acids may be redundant to normally nourished or slightly malnourished patients whose real problems are dehydration, anorexia and fatigue. On the other hand, when oral intake is disturbed, provision of merely water and basal electrolytes may lead to worsening of patient nutritional status. Therefore, administration of complete and practical maintenance solution, i.e. Aminofluid is a proactive approach to improve patients' general condition.

References:

- (1) Sunghyo Shin, Takenobu Kamada. Japanese Pharmacology & Therapeutics 1994;22
- (2) (Supplement):S937-947 Carol Braunschweig et al. Indications for Administration of Parenteral Nutrition in Adults Nutrition in Clinical Practice 19:255–262, June 2004.
- (3) Plank LD, Hill GL. Energy balance in critical illness. Proc Nutr Soc. 2003;62:545–552.

FATIGUE, A HIDDEN SYMPTOM OF HOSPITALIZED PATIENTS

Iyan Darmawan

Introduction

Unlike typical fatigue in a healthy person, which occurs as an indispensable sensation that prompts the desire to rest, in serious illness fatigue is disproportionate to exertion level and is not relieved by rest or sleep.

Researchers from England and Japan have recently fully clarified the mechanism of fatigue, known as central fatigue, implicated in Chronic Fatigue Syndrome

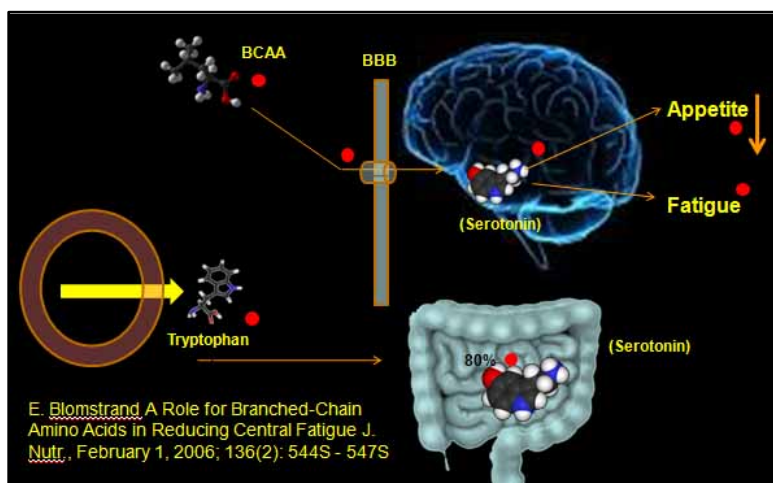
There are at least five metabolic causes of fatigue that have been reported in the medical literature. These include 1) a decrease in the phosphocreatine level in the muscle, 2) a proton accumulation in the muscle, 3) depletion of the glycogen store in muscles, 4) hypoglycemia and 5) an increase in the plasma concentration ratio of free tryptophan to branched-chain amino acids.

Is it common?

79 palliative patients were studied by Sigurdardottir. They reported dyspnea and lack of wellbeing (70%), dry mouth (58%), fatigue (56%), depression (41%), anxiety (37%), pain at rest (30%), and pain on movement (42%).⁽¹⁾

Role of Tryptophan in Central Fatigue

Tryptophan is the precursor for the neurotransmitter 5-hydroxytryptamine (5-HT), which is involved in fatigue and sleep. It is present in bound and free form in the blood, where the concentration is controlled by albumin binding to tryptophan. An increase in plasma free tryptophan leads to an increased rate of entry of tryptophan into the brain. This should lead to a higher level of 5-HT which may cause central fatigue.



Central fatigue is implicated in clinical conditions such as chronic fatigue syndrome and post-operative fatigue. Increased plasma free tryptophan leads to an increase in the plasma concentration ratio of free tryptophan to the branched chain amino acids (BCAA) which compete with tryptophan for entry into the brain across the blood-brain barrier.

Mechanism of Fatigue

The basic mechanisms of fatigue have been broadly categorized into two main components: peripheral and central. Peripheral fatigue, which occurs in the neuromuscular junctions and muscle tissues, results in the inability of the peripheral neuromuscular apparatus to perform a task in response to central stimulation. Mechanisms implicated in peripheral fatigue include a lack of ATP and the buildup of metabolic by-products.

Central fatigue, which develops in the central nervous system (CNS), arises from the progressive failure to transmit motor neuron impulses. Central fatigue has been defined as difficulty in the initiation or maintenance of voluntary activities. Central fatigue thus manifests as "a failure to complete physical and mental tasks that

require self-motivation and internal cues, in the absence of demonstrable cognitive failure or motor weakness" ⁽²⁾

POSTOPERATIVE FATIGUE

The plasma concentrations of these amino acids were measured in patients undergoing major surgery (Yamamoto et al., 1997).. In post-operative recovery after major surgery plasma free tryptophan concentrations were markedly increased compared with baseline levels; the plasma free tryptophan/BCAA concentration ratio was also increased after surgery.

Plasma albumin concentrations were decreased after surgery: this may account for the increase in plasma free tryptophan levels. It is suggested that BCAA supplementation may help to counteract the effects of an increase in plasma free tryptophan, and may thus improve the status of patients during or after some clinically stressful conditions. ^(3,4)

There was a significant correlation between fatigue scores and plasma free tryptophan ($P < 0.000$), and the plasma concentration ratio of free tryptophan/BCAA ($P < 0.016$) after surgery in all the patients studied ($n = 34$). This correlation was more marked in the colorectal-surgery patients, in whom surgery was more severe.

These data provide further evidence of a possible biochemical mechanism for central fatigue which involves a precursor of 5-HT. The provision of branched chain amino acids may help to combat the surge in free tryptophan that occurs during stress such as major surgery ⁽⁵⁾.

After even uncomplicated surgery patients can feel tired and washed out for several months. They often need to sit or lie down, and need to sleep more. Most severe illness, like serious infection, does this, so it is not unexpected. But neither is it understood nor is it well studied. ⁽⁶⁾

POST HYSTERECTOMY

DeCherney et al completed a telephone survey of 300 women aged 25-50 who had undergone a hysterectomy or myomectomy within the past 2 years.. RESULTS: Overall, 74% of patients experienced moderate-to-severe fatigue within the first few weeks after surgery.

Fatigue occurred more frequently and persisted twice as long as pain, the next most frequent symptom, which was experienced by 63% of patients overall. Fatigue was the symptom that most interfered with daily activities (37%) and also contributed to feelings of frustration (52%), to depression (37%), and to difficulty in concentrating (42%). Patients employed at the time of surgery missed an average of 5.8 weeks of work; 69% of those surveyed required 2 or more weeks of caregiver assistance.. CONCLUSIONS: Fatigue is a highly prevalent posthysterectomy and myomectomy symptom and has substantial negative physical, psychosocial, and economic effects on patients during recovery.⁽⁷⁾

BRANCHED-CHAIN AMINO ACIDS

The branched-chain amino acids (BCAAs) leucine, isoleucine and valine are primarily metabolized in the skeletal muscle as energy substrate or are used as precursors of the synthesis of other amino acids and proteins. These BCAAs exert a significant influence on the metabolism of glutamine and together serve as an important energy substrate for the brain, kidneys, liver and heart. The increased BCAA concentration in the skeletal muscle reduces glutamate dehydrogenase activity, thereby limiting glutamine degradation. Intracellular glutamate plays a central role in the preservation of high-energy phosphates in muscle, and its low intramuscular levels have been correlated with early lactic acidosis during exercise. Infusion with BCAAs stimulates synthesis and decreases protein degradation, thereby regulating muscle renovation.

During prolonged exercises, BCAAs can constitute an oxidative substrate for the skeletal muscles. Under conditions of relative energy shortfalls, such as those induced by sepsis, trauma and hypoxia, the BCAA metabolism is accelerated in the skeletal muscle ⁽⁸⁾.

CONCLUSION

Fatigue is an important symptom in hospitalized patients yet often overlooked by doctors. The recognition and understanding of the mechanisms involved may help improve the quality of patient management. Since serotonin and its precursor, i.e tryptophan are implicated as well in the pathophysiology of postoperative fatigue, there is strong rationale of providing BCAA-enriched amino acid solution to surgical patients in addition to carbohydrate and electrolytes. Practical and complete formulation (e.g Aminofluid) can preferably be used for this purpose.

References:

1. Sigurdardottir KR, Haugen DF. Prevalence of distressing symptoms in hospitalised patients on medical wards: A cross-sectional study *BMC Palliative Care* 2008, 7:16 (23 September 2008)
2. Ryan JL, Carroll JK, Ryan EP et al. Mechanisms of cancer-related fatigue. *The Oncologist* 2007;12(suppl 1):22–34.
3. Castell LM, Yamamoto T, Phoenix J, Newsholme EA. The role of tryptophan in fatigue in different conditions of stress. *Adv Exp Med Biol.* 1999;467:697-704.
4. Yamamoto T, Castell LM, Botella J, Powell H, Hall GM, Young A, Newsholme EA. Changes in the albumin binding of tryptophan during postoperative recovery: a possible link with central fatigue? *Brain Res Bull.* 1997;43(1):43-6. Erratum in: *Brain Res Bull* 1997;44(6):735
5. McGuire J et al. Biochemical markers for post-operative fatigue after major surgery *Brain Research Bulletin* 60 (2003) 125–130. Elsevier Science Inc

6. GJ Rubin, M Hotopf. Systematic review and meta-analysis of interventions for postoperative fatigue. *British Journal of Surgery* 2002 89: 971-984.
7. DeCherney AH, Bachmann G, Isaacson K, Gall S. Postoperative fatigue negatively impacts the daily lives of patients recovering from hysterectomy. *Obstet Gynecol.* 2002 Jan;99(1):51-57
8. Debora Strose Villaça et al. New treatments for chronic obstructive pulmonary disease using ergogenic aids *J. bras. pneumol.* vol.32 no.1 São Paulo Jan./Feb. 2006

CANCER-RELATED FATIGUE (CRF)

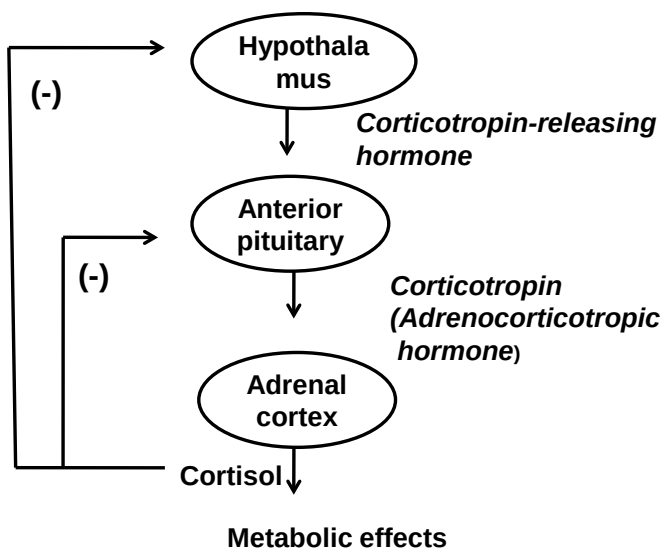
Budhi Santoso

Fatigue is highly prevalent in patients with cancer and it has a significant impact on patients' quality of life (QoL) and ability to carry out normal daily activities. The most commonly used definition of cancer-related fatigue (CRF) was developed by the National Comprehensive Cancer Network (NCCN) Fatigue Guidelines Committee several years ago. The Committee characterized CRF as "an unusual, persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning" ⁽¹⁾. The basic mechanisms of fatigue have been broadly categorized into two main components: peripheral and central ⁽²⁾. Peripheral fatigue, which occurs in the neuromuscular junctions and muscle tissues, results in the inability of the peripheral neuromuscular apparatus to perform a task in response to central stimulation. Mechanisms implicated in peripheral fatigue include a lack of ATP and the buildup of metabolic by-products. Central fatigue, which develops in the central nervous system (CNS), arises from the progressive failure to transmit motor neuron impulses ⁽³⁾. Central fatigue has been defined as difficulty in the initiation or maintenance of voluntary activity. Central fatigue thus manifests as "a failure to complete physical and mental tasks that require self-motivation and internal cues, in the absence of demonstrable cognitive failure or motor weakness"⁽⁴⁾.

1. HPA-Axis Dysfunction and Cancer-Related Fatigue

Another potential etiology of fatigue is the disturbance of the HPA axis. Low levels of circulating cortisol have been observed in patients with chronic fatigue syndrome. The HPA-axis dysfunction hypothesis proposes that cancer, and/ or cancer treatment, alters the function of the HPA axis, resulting in endocrine changes that cause or contribute to fatigue ⁽⁵⁾. The HPA axis is the central

regulatory system controlling release of the stress hormone cortisol. Cortisol exerts a multitude of biological effects, including regulation of blood pressure, cardiovascular function, carbohydrate metabolism, and immune function. Cortisol also exerts a negative feedback on the HPA axis at the level of the hippocampus, hypothalamus, and pituitary. Serum cortisol concentrations show diurnal variation, typically being highest after waking and then declining throughout the day.



2. Serotonin Dysregulation

One hypothesis proposed to explain CRF is that cancer and/ or cancer treatment causes an increase in brain serotonin (5-HT) levels and/or upregulation of a population of 5-HT receptors, leading to reduced somatomotor drive, modified hypothalamic–pituitary–adrenal (HPA) axis function, and a sensation of reduced capacity to perform physical work ⁽⁶⁾. 5-HT has numerous functions, including control of appetite, sleep, memory,

learning, temperature regulation, mood, behavior, cardiovascular function, muscle contraction, endocrine regulation, and depression, and there is increasing evidence for a role for 5-HT in the genesis of central fatigue. In particular, research in exercise-induced fatigue and chronic fatigue syndrome implicates 5-HT dys-regulation in the etiology of central fatigue.

3. 5-HT Levels and Central Fatigue

Studies in patients with chronic fatigue syndrome have demonstrated raised plasma levels of free tryptophan, which could potentially lead to high central 5-HT levels ⁽⁷⁾. The rate-limiting step for synthesis of 5-HT in the brain is the transport of tryptophan into the brain. Tryptophan and branched-chain amino acids (BCAAs) compete for entry into the brain via a transporter. During exercise, BCAAs are taken up by muscle cells. One hypothesis suggests that increased levels of central 5-HT during exercise are caused by a reduction in circulating BCAAs, which allows more tryptophan to enter the brain. From studies in humans, Blomstrand and colleagues ⁽⁸⁾ and Mittleman and colleagues ⁽⁹⁾ reported that supplementation with BCAAs before and during exercise was associated with improved physical and mental performance.

4. Changes in 5-HT Receptors and Fatigue

Changes in 5-HT receptors may also contribute to fatigue. Patients with chronic fatigue syndrome may have enhanced serotonergic responses, possibly due to upregulation and/or hypersensitivity of postsynaptic 5-HT_{1A} receptors in the hypothalamus ⁽¹⁰⁾. Cleare and colleagues ⁽¹¹⁾ have also reported evidence of decreased 5-HT_{1A} receptor numbers or affinity in chronic fatigue syndrome. Other evidence suggests a disruption of the interaction between the HPA axis and the serotonergic system in chronic fatigue syndrome. This disrupted interaction may arise either from decreased

responsiveness of the 5-HT_{1A} receptors responsible for controlling the HPA axis at the hypothalamic level or from reduced pituitary responsiveness.

5. Dysregulation of Central 5-HT Metabolism and Cancer-Related Fatigue

Dysregulation of central 5-HT metabolism or function may be a contributing factor in CRF. There is evidence that proinflammatory cytokines, such as tumor necrosis factor (TNF)- α , can influence 5-HT metabolism. Evidence suggests the existence of a feedback loop between TNF- α and central 5-HT ⁽¹²⁾ in which peripherally synthesized TNF- α causes an increase in 5-HT release into the synaptic space. In addition, TNF- α can increase 5-HT transporter function, resulting in increased clearance of 5-HT from the synaptic space. Conversely, 5-HT can decrease TNF- α synthesis. The feedback loop in the CNS may become dysregulated in patients with pathologic conditions or in response to cancer therapies.

6. Cytokine Dysregulation

Proinflammatory cytokines, such as TNF- α and IL-1 β , are implicated in many of the mechanisms proposed for the etiology of fatigue associated with cancer and various illnesses ⁽¹³⁾. Experimental or therapeutic administration of proinflammatory cytokines is known to induce "sickness behavior". In particular, TNF has been shown to be associated with alterations in CNS neurotransmission, leading to behavioral changes such as lethargy and anorexia. Cancer and its treatment (chemotherapy, surgery, radio-therapy, biologic therapies) are associated with increases in plasma levels of cytokines, especially TNF- α , IL-1 β , and IL-6 . One published clinical study has examined possible correlations between serum cytokine levels and fatigue in patients with cancer ⁽¹⁴⁾. Future research needs to focus on understanding the interrelationships among the

various cancer-related symptoms and the similarities and differences in fatigue experienced in different conditions.

References:

1. Morrow, R Gary; Cancer-Related Fatigue: Causes, Consequences, and Management; The Oncologist, Vol. 12, No. suppl_1, 1-3, May 2007;
2. Julie L. Ryan^{a,b}, Jennifer K. Carroll^{b,c}, Elizabeth P. Ryan^{b,d}, Karen M. Mustian^b, Kevin Fiscella^{c,e}, Gary R. Morrow^{b,f}, Mechanisms of Cancer-Related Fatigue; The Oncologist, Vol. 12, No. suppl_1, 22-34, May 2007;
3. Gandevia SC. Spinal and supraspinal factors in human muscle fatigue. *Physiol Rev* 2001;81:1725–1789.
4. Chaudhuri A, Behan PO. Fatigue in neurological disorders. *Lancet* 2004;363:978–988
5. Cleare AJ. The neuroendocrinology of chronic fatigue syndrome. *Endocr Rev* 2003;24:236–252.
6. Andrews PLR, Morrow GR, Hickok JT et al. In: Armes J, Krishnasamy M, Higginson I, eds. *Fatigue in Cancer. Mechanisms and models of fatigue associated with cancer and its treatment: Evidence of pre-clinical and clinical studies.* Oxford: Oxford University Press, 2004:51-87.
7. Badawy AA, Morgan CJ, Llewelyn MB et al. Heterogeneity of serum tryptophan concentration and availability to the brain in patients with the chronic fatigue syndrome. *J Psychopharmacol* 2005;19:385–391.
8. Blomstrand E. A role for branched-chain amino acids in reducing central fatigue. *J Nutr* 2006;136(suppl):544S–547S.
9. Mittleman KD, Ricci MR, Bailey SP. Branched-chain amino acids prolong exercise during heat stress in men and women. *Med Sci Sports Exerc* 1998;30:83–91.
10. Bakheit AM, Behan PO, Dinan TG et al. Possible upregulation of hypothalamic 5-hydroxytryptamine receptors in patients with postviral fatigue syndrome. *BMJ* 1992;304:1010–1012.
11. Cleare AJ, Messa C, Rabiner EA et al. Brain 5-HT_{1A} receptor binding in chronic fatigue syndrome measured using positron emission tomography and [¹¹C]WAY-100635. *Biol Psychiatry* 2005;57:239–246
12. Morrow GR, Andrews PLR, Hickok JT et al. Fatigue associated with cancer and its treatment. *Support Care Cancer* 2002;10:389–398.

13. Konsman JP, Parnet P, Dantzer R. Cytokine-induced sickness behaviour: Mechanisms and implications. *Trends Neurosci* 2002;25:154–159
14. Pusztai L, Mendoza TR, Reuben JM et al. Changes in plasma levels of inflammatory cytokines in response to paclitaxel chemotherapy. *Cytokine* 2004;25:94–102.

FLUID AND ELECTROLYTES IN CANCER PATIENTS

Iyan Darmawan

Fluid and electrolyte abnormalities are common in patients with cancer. The etiology may be common to all patient populations or be specific to cancer patients. Hyponatremia is frequently hypovolemic due to renal loss of sodium from diuretics or salt-wasting nephropathy as seen with some chemotherapeutic agents such as cisplatin. Cerebral salt wasting also can occur in patients with intra- cerebral lesions.⁽¹⁾

Normovolemic hyponatremia may occur in association with SIADH from cervical cancer, lymphoma, and leukemia, or from certain chemotherapeutic agents. Hypernatremia in cancer patients is most often due to poor oral intake or gastrointestinal volume loss (ileus, obstruction). Central DI can also lead to hypernatremia in patients with central nervous system lesions.^(1,2)

SIADH Criteria⁽²⁾

- A fall in plasma osmolality
- An inappropriately elevated urine osmolality (above 100 mOsm/kg and usually above 300 mOsm/kg)
- Urine Sodium concentration usually above 30 mmol/L
- A relatively normal to low plasma urea and creatinine concentration
- Normal adrenal and thyroid function

Hypokalemia can develop from gastrointestinal losses associated with diarrhea due to radiation enteritis or chemotherapy, or directly from tumors such as villous adenomas of the colon. Tumor lysis syndrome can precipitate severe hyperkalemia from massive cell destruction.

In hospitalized patients malignancy is the most frequent cause of hypercalcemia, and conversely, hypercalcemia

is the most frequently occurring electrolyte problem of cancer patients⁽³⁾

Hypocalcemia can be seen following removal of a thyroid or parathyroid tumor or following a central neck dissection by damage to the parathyroid glands. Hungry bone syndrome produces acute and profound hypocalcemia following parathyroid surgery for secondary or tertiary hyperparathyroidism when calcium is rapidly taken up by bones. Prostate and breast cancer can result in increased osteoblastic activity that increases bone formation thereby decreasing serum calcium. Acute hypocalcemia also can occur with hyperphosphatemia as phosphorus complexes with calcium. Hypomagnesemia is a side effect of ifosfamide and cisplatin therapy. Hypophosphatemia can be seen with hyperparathyroidism as phosphorus reabsorption is decreased, while oncogenic osteomalacia increases urinary excretion of phosphorus. Other causes of hypophosphatemia in cancer patients include renal tubular dysfunction from multiple myeloma, Bence Jones proteins, and certain chemotherapeutic agents. Acute hypophosphatemia can occur as rapidly proliferating malignant cells take up phosphorus in acute leukemia or from hungry bone syndrome following parathyroidectomy. Tumor lysis syndrome or bisphosphonates (used in the treatment of increased calcium) can also cause hyperphosphatemia.

Malignancy is the most common etiology of hypercalcemia in hospitalized patients and is due to increased bone resorption or decreased renal excretion. Bone destruction occurs from bony metastasis as seen with breast or renal cell cancer, but also can occur with multiple myeloma. With Hodgkin's and non-Hodgkin's lymphoma, hypercalcemia results from increased calcitriol formation, which in turn increases absorption of calcium from both the gastrointestinal tract and bone.

Humoral hypercalcemia of malignancy is a common cause of hypercalcemia in cancer patients. As parathyroid-related protein is secreted, it binds to parathyroid receptors, stimulating calcium resorption from bone and decreasing renal excretion of calcium.

The treatment of hypercalcemia of malignancy should begin with saline volume expansion. This alone will decrease renal reabsorption of calcium as the associated volume deficit is corrected. Once an adequate volume status has been achieved, a loop diuretic may be added. Unfortunately, these measures are only temporary and additional measures need to be taken. A variety of drugs are available with varying times of onset, duration of action, and side effects. Bisphosphonates (etidronate and pamidronate) inhibit bone resorption and osteoclastic activity. They act slowly (within 48 hours) but last for up to 15 days. Calcitonin also is effective by inhibiting bone resorption and increasing renal excretion of calcium. It acts quickly (within 2 to 4 hours), but its use is limited by the development of tachyphylaxis. Corticosteroids may decrease tachyphylaxis and can be used alone to treat hypercalcemia. Gallium nitrates are potent inhibitors of bone resorption. They display a long duration of action but can cause nephrotoxicity. Mithramycin is an antibiotic that blocks osteoclastic activity but can be associated with liver, renal, and hematologic abnormalities, and therefore its use is limited to the treatment of Paget's disease of the bone. For patients in whom hypercalcemia is severe and refractory, or who are unable to tolerate volume expansion (due to pulmonary edema or congestive heart failure), dialysis is an option.⁽²⁾

Tumor lysis syndrome results when the release of intracellular metabolites is greater than the kidneys' excretory capacity. A rapid release of uric acid, potassium, and phosphorus occurs and is associated

with marked hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and acute renal failure.

It is typically seen with poorly differentiated lymphomas and leukemias, but also can be seen with a number of solid tumor malignancies. Tumor lysis syndrome most commonly develops following treatment with chemotherapy or radiotherapy. Once it develops, volume expansion should be undertaken, as should correction of electrolyte abnormalities. Associated hypocalcemia should not be treated unless it is symptomatic, to avoid metastatic calcifications. Dialysis may be required for impaired renal function or for correction of electrolyte abnormalities.

Electrolyte abnormalities in chemotherapy-induced febrile neutropenia⁽⁴⁾

Sheik et al reported out of 215 patients undergoing chemotherapy for various cancers. Electrolyte abnormality of all grades combined was seen in 83% of patients. Hypokalemia, of any grade, was seen in 48% of patients. Among those 51.4% had grade I, 33.3% had grade III and 15.2% had grade IV hypokalemia. Hyponatremia of all grades was seen in 67.9% patients.. Hypomagnesaemia was seen in 54.3% patient.

References:

1. Brunicardi FC et al. Schwartz's Principles of Surgery, 8th Edition
2. Onitilo AA Kio E, and Suhail A. R. Doi, Tumor-Related Hyponatremia Clin Med Res. 2007 December; 5(4): 228–237
3. Dafnis EK, Laski ME. Fluid and Electrolyte Abnormalities in the Oncology Patient. Seminars in Nephrology, Vol 13, No 3 (May), 1993 pp 281-296
4. Asim Jamal Shaikh et al. Incidence and Impact of Baseline Electrolyte Abnormalities in Patients Admitted with Chemotherapy Induced Febrile Neutropenia *J Cancer* 2011; 2:62-66

MONITORING OF PARENTERAL FLUID THERAPY

Iyan Darmawan

Introduction

The administration of intravenous therapy subjects the patients to numerous risks, such as local or systemic complications. Local complications, such as phlebitis, infiltration and cannula occlusion, occur more frequently than systemic complications, which include hyperglycemia, septicemia, circulatory overload, and embolism. For this reason, monitoring and catheter care are critical components of intravenous administration.

I MONITORING OF PERIPHERAL SITES

The parameters to be monitored include: the fluid container, the administration tubing, the flow rate, the electronic infusion device (if used), the intravenous site dressing, the vascular access device, and the insertion site. The frequency for monitoring a peripheral intravenous site depends on the prescribed therapy, the condition and age of the patient. Intravenous sites should be monitored at 1-2 hour intervals. The pediatric, geriatric and critically-ill patient requires more frequent site assessment. ⁽¹⁾

Fluid container

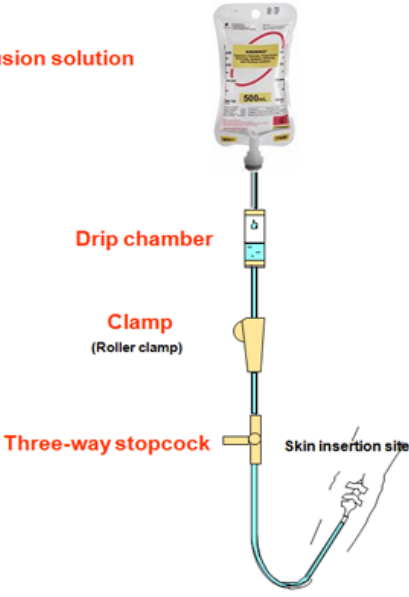
A systematic assessment begins with the fluid container and progresses down the tubing to the vascular access device and the insertion site. The type of solution and the medication added are verified against the physician's order, as is the information printed on the fluid container label. The container must be labeled with the date and time that it was hung. Containers can be labeled with times they are hung and flow levels in many ways. The label should not be placed over important information printed on the solution container. Fluid container should

not be labeled by writing with a pen or marker on plastic surface, because the ink can penetrate the plastic and leak into the intravenous solution. Then take note the amount of solution remaining in the container. Nurse determines how much fluid should remain in the fluid container based on the prescribed flow rate and the indicated time. We should be aware that infusion sets from various manufacturers may have different drip amount per ml (either 15 drops or 20 drops per ml). For example, with infusion set of 15 drops/ml, if you administer the infusion solution at a rate of 20 drops/minute it corresponds to 80 ml per hour. The appearance is also noted: it should be clear and free from cloudiness and particulate matters. Solutions contained in glass bottles require vented intravenous tubing or air needle.

Tubing

Correct tubing should be hanging with the fluid container and the electronic infusion device. When a gravity infusion set is used, the height of the fluid container should be placed 30 to 36 inches (76-100 cm) above the patient. Raising the height of the container increases the flow rate. The flow rate can also be altered by any change in the patient's position. If the puncture site is located on an extremity near a point of flexion, any time the patient bends an arm or wrist, the flow rate is altered and can result in inaccurate delivery of fluids and medication. Several other factors can alter flow rate, as follows:

- Viscosity of fluids : blood, lipid, or colloidal solutions (eg albumin and dextran). It may be necessary to use a larger-gauge cannula and avoid very small vein (eg dorsal hand vein)
- Temperature of solutions: cool solution can induce venous spasm and slows the flow rate
- Undetected infiltration, phlebitis or thrombus

	Remaining amount: Is the solution being administered as instructed? Descriptions: Is there any sign of decomposition due to addition of other drugs? Is the solution exposed to sunlight? Is the solution hung at the appropriate height? (Is the air needle inserted?) Are the drip rate and the volume of fluid in the chamber appropriate?
---	---

Is the drip rate altered? (body movement may affect the drip rate)

Make fine adjustments considering the height of the stand.

Is the position of the cock of the three-way stopcock correct?

Is it covered properly?

Is there loosening of or a leak from the three-way stopcock connection?

Is the infusion route bent or compressed?

Is it fixed securely? Is there a rash from taping?

Is there a leak, flare, or swelling at the insertion site?

Is there any symptom of phlebitis?

Adapted from: Susumu Tanaka, Saishin Jouchu Manual, p46, Shorinsha Inc., 1996 (modified)

Intravenous site dressing

The dressing is monitored to ensure that it remains dry, closed and intact. An intact dressing means that all

edges are sealed to the skin. If the dressing is damp or the integrity is compromised, it must be changed immediately. A transparent dressing is available nowadays and offers the advantages of possibility of detecting early signs of phlebitis and infiltration.

Insertion Site

Blanching

Blanching is a white, shiny appearance at the insertion site. It is an indicator of an infiltration, or a fluid leak into the tissue. If any fluid leakage is noted at the insertion site, the intravenous site should be restarted. Separate discussion on infiltration and phlebitis is also written in this handbook.

II MONITORING OF METABOLIC COMPLICATIONS

The metabolic complications related to parenteral nutrition can be serious, but they can be minimized with adequate monitoring. Acute metabolic complications include electrolyte deficiencies, particularly potassium, magnesium, phosphorus, and calcium. These deficiencies are common but can be prevented by adequate monitoring of plasma levels. The same is true for trace elements and vitamin deficiencies, particularly thiamine. Excess glucose can aggravate hyperglycemia, which has been associated with poor outcome after cardiac surgery, myocardial infarction, and stroke and an impaired leukocyte function contributing to an increased nosocomial infection rate. Hypertriglyceridemia can increase the risk for liver steatosis. Infusion of lipids during a period of 4 to 8 hours can result in pulmonary hypertension. Serum triglyceride levels should be determined before parenteral nutrition is started and once a week thereafter. When parenteral nutrition is instituted, patients with renal failure are more susceptible to uremia and those with volume depletion to metabolic acidosis. ⁽²⁾

In this article, only acute metabolic complication will be highlighted.

Definition of relevant acute metabolic complications

(3)

Complications	Evidence
Hyperglycemia	>12 mmol/L (even this may be too high)
Hypoglycemia	< 3 mmol/L
Ketoacidosis	Arterial pH < 7.3 + > 2 dipstick for urinary or serum ketones
Hyperosmolar hyperglycemic non ketosis	Very high blood glucose + serum osmolarity > 305 mOsm/L + absence of urinary ketones
Sodium, potassium, chloride, ionised calcium, magnesium, phosphate disorders	Serum values outside the reference range
Hypertriglyceridemia	>150% of upper reference limit measured > 8 h after lipid emulsion (check milky plasma)
Hyperazotemia ^a	>twice upper limit of reference
Hyperchloremic acidosis	Serum Cl ⁻ > 115 mmol/L + arterial pH < 7.3
Hepatic dysfunction, AST, ALT, ALP, bil	>twice the upper reference limit
Fluid overload	Heart failure, edema or weight gain > 0.45 kg/d for 3 or more consecutive days
Coagulopathy	Prothrombin time and/or partial thromboplastin time > 150% of upper limit of reference

a Concentrations >twice baseline values may reflect nutrient overload. Adapted from Buzby et al. Am J Clin Nutr 1988;47:366–81

SUGGESTED MONITORING SCHEDULE FOR PATIENTS RECEIVING PARENTERAL NUTRITION ⁽⁴⁾

Variable	Initial Period[<u>±</u>]	Later Period[<u>±</u>]
----------	----------------------------	--------------------------

BUN/creatinine	2 times/wk	Weekly
Albumin or prealbumin	Weekly	Weekly
Ca ²⁺ , Mg ²⁺ , P	2 times/wk	Weekly
ALT, AST, ALP	Weekly	Weekly
Total and direct bilirubin	Weekly	Weekly
Electrolytes and glucose	Daily until stable	Weekly
CBC	Weekly	Weekly
Triglycerides	With each increase	Weekly
Vitamins	—	As indicated
Trace minerals	—	As indicated

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; CBC, complete blood count

[†]The period before nutritional goals are reached or during any period of instability. [‡] When stability is reached, no changes in nutrient composition.

Hyperglycemia

Hyperglycemia is an independent marker of poor inpatient outcomes in a variety of clinical settings, including acute coronary syndromes, cardiac surgery, stroke, and labor and delivery.

In otherwise non-diabetic patients hyperglycemia is seldom induced by parenteral glucose when the administration rate is max 4 mg/kg/minute. ^(5) If this rate is translated into ml/kg/hour it is 2.4 ml of 10% glucose/kg/hour or 3.2 ml of 7.5% glucose/kg/hour.

Therefore, a parenteral solution containing 7.5% glucose (eg Aminofluid®) will not induce hyperglycemia in a 60 kg patient as long as the administration rate is 80 ml/hour (which is far below max of 192 ml/hour).

The risk of inpatient hyperglycemia increases by medications: corticosteroids, gatifloxacin, atypical antipsychotics (with the exception of Abilify®), protease inhibitors, thiazide diuretics, niacin, lithium, rifampin,

phenytoin, and IV medications mixed in dextrose-containing solutions. ⁽⁶⁾

Hypertriglyceridemia

Patients taking TPN should have their plasma lipids (triacylglycerols) measured before and during TPN initiation. This is particularly important in patients who are at high risk of impaired fat clearance, such as those who are hyperlipidemic, diabetic, septic, or with impaired renal or hepatic function, or those who are critically ill ⁽⁷⁾

At present, there is a tendency to increase the glucose:fat calorie ratio from 50:50 to 60:40 or even 70:30 of the non-protein calories, due to the problems encountered regarding hyperlipidaemia and fatty liver, which is sometimes accompanied by cholestasis and in some patients may progress to non-alcoholic steatohepatitis (Grade C). ⁽⁸⁾

Exactly what disadvantages derived from fatty liver and hypertriglyceridaemia are unknown. In the vascular literature it is firmly established that hypertriglyceridemia is a risk factor for the development of arteriosclerosis and acute infusion of long-chain triglyceride (LCT) containing lipid emulsion diminishes the ability of the arterial vascular bed to relax. The main concern that these conditions impair immune response is not supported by a recent meta-analysis. However, most experts recommend avoiding a triglyceride level greater than 5 mmol/dL, although hard data supporting this are lacking. When this level is reached it is recommended by many experts in the field to diminish the fat content (especially n-6 poly-unsaturated fatty acids (PUFAs)) of the parenteral nutrition or temporarily to withdraw fat. In this event the energy deficit should not be replaced by adding more glucose because this may exceed the patient's oxidative capacity.

Conclusion

Good monitoring of parenteral fluid and nutrition therapy is at least as important as the selection of intravenous solution. Prevention and recognition of early signs of local and metabolic complications will facilitate recovery and avoid unnecessary cost shouldered by patients..

References

1. Perucca R. Intravenous Monitoring and Catheter Care. In Terry Judy. Intravenous Therapy: Clinical Principles and Practice. WB Saunders Company 1995
2. Goldman: Cecil Medicine, 23rd ed.; Chapter 236 - PARENTERAL NUTRITION
3. Sobotka L, Camilo ME. Basics in clinical nutrition: Metabolic complications of parenteral nutrition e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism 4 (2009) e120–e122
4. Johns Hopkins: The Harriet Lane Handbook, 18th ed.; Chapter 21 - Nutrition and Growth >> PARENTERAL NUTRITION (PN)
5. Mizock BA, Troglia S. Nutritional support of the hospitalized patient. Mosby Vol 53, No 6, 1997, p 367
6. Averett L, Salvatori R. Inpatient Management of Endocrinologic Disorders In Piccini & Nilsson: The Osler Medical Handbook, 2nd ed. Copyright © 2006 Johns Hopkins University
7. Crook MA. Lipid clearance and total parenteral nutrition: the importance of monitoring plasma lipids. Nutrition, Volume 16, Issue 9, September 2000, Pages 774-775
8. Braga M et al. ESPEN Guidelines on Parenteral Nutrition: Surgery Clinical Nutrition, Volume 28, Issue 4, August 2009, Pages 378-386

INCOMPATIBILITY OF INFUSION SOLUTION

Iyan Darmawan

Introduction

Nowadays with abundant injectables and infusion solutions in the market, knowledge about compatibility and incompatibility data for multiple intravenous drug delivery methods has become increasingly important.

A chance of incompatibility exists whenever any medication is combined or added to an IV fluid. It is important not only paying attention to the drugs themselves, but also to a variety of factors including the concentration, temperature, storage vehicle, infusion solution, order of mixing and administration technique¹

Three types of incompatibility are commonly known: physical, chemical and therapeutic. Physical incompatibilities are most easily observed and evidenced by visible changes, such as formation of particulates, haze, precipitation, colour change. Chemical incompatibilities result from loss of potency after a certain period and in most situations are not recognized by visual changes. Therapeutic incompatibility can be pharmacokinetic or pharmacodynamic interaction.

IV Drugs Incompatibility

Some injectable drugs are not compatible with the content of infusion solutions. Typical examples are Sodium Bicarbonate cannot be mixed into Lactated or Acetated Ringer Solutions because it can form calcium carbonate.

To prevent incompatibilities, it is important to consider all the ways in which medications may interact outside of or inside the body. If you must mix a medication, always

follow manufacturer's instructions as to the correct volume and type of diluent; which solutions it may be added to for "piggy back" administration; and what flush solutions must be used in between administrations to prevent events like precipitation within the patient's access device (for example, never administer phenytoin into an intravenous line containing dextrose, or never allow amphotericin B to come into contact with saline solutions). Other issues to consider are the presence of electrolytes (e.g. potassium chloride) mixing into continuous infusions, such as in a piggyback situation. If mixing medications in a syringe for bolus administration (IV push), assure that they are compatible when combined in a syringe. If consulting a drug reference is not helpful, contact the pharmacy, which has access to additional compatibility information.

Be on alert for medications with a known history of frequent incompatibilities when they come into contact with other drugs. Among the drugs most often incriminated in incompatibilities are furosemide (Lasix), phenytoin (Dilantin), heparin, midazolam (Versed), and diazepam (Valium) when used in IV admixtures.

Drawbacks of PVC ²

In addition to IV drugs compatibility, clinicians should know that some important issues arise when using PVC as container of infusion solutions. Plasticized polyvinyl chloride (PVC) is one of the most widely used polymeric materials in medical and related fields. In the medical field, flexible PVC is used for the blood storage bags, blood tubing used during hemodialysis, endotracheal tubes, intravenous solution dispensing sets, as well as for drug product storage and packaging. PVC is a rigid polymer, so plasticizers are added to increase its flexibility. Phthalic acid esters, mainly di-(2-ethylhexyl) phthalate (DEHP), are the most preferred plasticizers used in the medical field. Since these additives are not covalently bound to the polymer, there is a possibility for

migration of the plasticizer from the matrix. The migration of DEHP from the PVC bags into the solution has been a major concern for many years. The toxicity of DEHP and PVC has raised serious questions about their use. This separation of DEHP from the PVC is called leaching. Leaching occurs when some drugs such as paclitaxel or tamoxifen are administered in PVC bag.

Another concern of using PVC bags are sorption and loss of drug from PVC bags:

- Kowaluk et al.³ examined interactions between 46 injectable drug products and Viaflex (PVC) infusion bags. Study results showed that sorption increases as drug concentration increases
- Migration of drug into plastic may lead to subtherapeutic drug concentrations eg. insulin, vit A, acetate, diazepam and nitroglycerin.

In addition. PVC bags are not suitable containers for infusion admixtures containing many lipophilic drugs, such as diazepam and midazolam hydrochloride in neutral media. Despite their own lipophilicity, polyolefine (polyethylene and polypropylene) bags appear more suitable⁴

Maillard Reaction

The term 'nonenzymatic browning' refers to the chemical reactions that result in the formation of brown color when food is heated. In contrast to enzymatic browning, no enzymes are involved in nonenzymatic browning reactions. The most important nonenzymatic browning reaction is the Maillard reaction, which encompasses the cascade of reactions that occur when reducing sugars are heated with compounds possessing a free amino group (e.g., amino acids, amines, and proteins) and which result in many reaction intermediates and products.

The Maillard reaction is named after the French scientist, Louis Camille Maillard, who first investigated reducing sugar–amino acid interactions in 1912. Other nonenzymatic browning reactions include Maillard-type reactions between amino compounds and other compounds possessing a free carbonyl group, e.g., ascorbic acid and lipid oxidation products.⁵

Although it is not drug-drug interaction, it is important to address this issue. The Maillard reaction is a chemical reaction between an amino acid and a reducing sugar, usually requiring heat. Like caramelization, it is a form of non-enzymatic browning. The reactive carbonyl group of the sugar reacts with the nucleophilic amino group of the amino acid, and forms a variety of interesting but poorly characterized molecules responsible for a range of odors and flavors. Maillard reaction occurs when amino acids and glucose are contained in single bag. Since amino acids and glucose should be given simultaneously, a clever approach is to produce a dual-chamber bag where glucose and amino acids are separated. They are premixed prior to administration.^{6,7}

References:

1. Cayo L. Compatibility of commonly used intravenous drugs. Pharmacy practice news, September 2011. McMahon Publishing.
2. Bridges J et al. The safety of medical devices containing DEHP-plasticized PVC or other plasticizers on neonates and other groups possibly at risk © European Commission 2007
3. Kowaluk EA, Roberts MS, Blackburn HD, Polack AE. Interactions between drugs and polyvinyl chloride infusion bags. *Am J Hosp Pharm.*1981;38(9):1308-14
4. Ch. B. Airaud,*t A. Gayte-Sorbiert and Ch. Bianchi Compatibility of diazepam (Valium@), clorazepate dipotassium salt (Tramenem) and midazolam hydrochloride(Hypnovel@) with Stedim 6@, a new multilayer polyethylene-lined film for infusion bags: a comparative study with polyvinyl chloride bagsJournal

of Clinical Pharmacy and Therapeutics Volume 18,
Issue 6, Article first published online: 28 JUN 2008

5. Ames JM. Nonenzymatic Browning. Copyright 2003, Elsevier Science Ltd, p
6. Larry K. Fry and Lewis D. Stegink Formation of Maillard Reaction Products in Parenteral Alimentation Solutions J. Nutr. 1982 112: 1631-1637
7. Stadler RH, Blank I, Varga N, Robert F, Hau J, Guy PA, Robert MC, Riediker S. Acrylamide from Maillard reaction products. Nature. 2002 Oct 3;419(6906):449-50.

PHLEBITIS, WHAT CAUSES AND HOW TO MANAGE?

Iyan Darmawan

Introduction

Phlebitis simply means inflammation of a vein. Severe phlebitis is almost always accompanied by a blood clot, or thrombus, in the affected vein, a condition known as thrombophlebitis. In more technical term, phlebitis refers to the clinical finding of pain, tenderness, swelling, induration, erythema, warmth and palpable cord-like veins due to inflammation, infection, and/or thrombosis.

Many factors have been implicated in the pathogenesis of phlebitis, namely: (1) chemical factors such as irritant drugs and fluids; (2) mechanical factors such as catheter material, size, site and duration of cannulation; and (3) infectious agents. Patient factors that may affect the rate of phlebitis include age, gender and underlying conditions (i.e. diabetes mellitus, infections, burns)⁽¹⁾.

Another cause which may skip attention is the presence of microparticulate in the infusion solutions and can be removed by in-line filtration⁽²⁾

Phlebitis is still an important and ongoing problem in medical practice. In patients with diabetes mellitus and infectious diseases, more attention is needed.⁽¹⁾

How common is infusion-related phlebitis?

The incidence of infusion-related phlebitis greatly varies by investigators, clinical settings and patient characteristics.

Incidence of Phlebitis	Author	Remark
35 %	Pose-Reino et.al ⁽³⁾	Infusion Phlebitis in Patients in a General Internal Medicine Service

Incidence of Phlebitis	Author	Remark
18%	Nordenström J, Jeppsson B, Lovén , Larsson J. ⁽⁴⁾	83 surgical patients were given PPN All nutrient solutions were delivered over a 12-h period from a 3-liter bag and the infusion sites rotated daily.,
26%	Nassaji-Zavareh M, Ghorbani.R. ⁽¹⁾	300 patients admitted to medical and surgical wards
39%	Manuel Monreal et al ⁽⁵⁾	Seven hundred sixty-six consecutive patients with acute pneumonia receiving IV therapy
35%	Joan Webster et al. ⁽⁶⁾	755 patients

Phlebitis has multifactorial causes as mentioned above ⁽⁷⁾

CHEMICAL PHLEBITIS

1. Extreme pH and osmolarity are always associated with the increased risk of phlebitis. The pH of dextrose solution ranges from 3 – 5 , the acidity being necessary to prevent caramelization of dextrose during autoclaving. Thus, glucose-containing solutions, amino acids and lipid emulsions used in parenteral nutrition are far more phlebitogenic than is normal saline. Injectable drugs that can produce severe venous inflammation, include potassium chloride, vancomycin, amphotericin B, cephalosporins, diazepam, midazolam and many chemotherapeutic agents. Infusion solutions having osmolarity higher than 900 mOsm/L should be administered via central line.
2. Microparticulates which are formed when medication particles are not fully dissolved during the mixing

process can also contribute to phlebitis. Thus when i.v. medications are administered the problem can be eliminated by the use of 1 to 5 μm filters.

3. Use of more proximal vein (cubital or forearm) for insertion is highly recommended for infusion solutions with osmolarity $> 500 \text{ mOsm/L}$. Avoid veins at dorsal hand if possible, particularly in elderly patients.



Don't use dorsal hand vein when you administer: Amino acids + glucose; Glucose + electrolytes; D5 or NS premixed with injectable drugs, eg. Meylon etc

4. Catheters made from silicone and polyurethane induce less irritation than polytetrafluoroethylene (Teflon) because they have smoother microsurface, are more thermoplastic, more flexible. Highest risk is associated with catheters made of PVC (polyvinyl chloride) or PE (polyethylene).
5. It was thought that slow infusion rate to cause less venous irritation than rapid rate.

MECHANICAL PHLEBITIS

Mechanical phlebitis is associated with the placement of cannula. Cannulas placed in flexion areas often result in the development of mechanical phlebitis. Cannula size

should be chosen to match the size of the vein and properly fixed.

BACTERIAL PHLEBITIS

Factors contributing to bacterial phlebitis include:

- 1) Poor handwashing technique
- 2) Failure to check equipment for compromised integrity.
Leaked or torn outer wrap invites bacteria.
- 3) Poor aseptic technique
- 4) Poor cannula insertion technique
- 5) Extended cannula dwell time
- 6) Infrequent inspection of i.v. site

Which patients are more prone to infusion-related phlebitis?

Predisposing factors

Nassaji-Zavareh M, Ghorbani.R studied the incidence of phlebitis in 300 hundred patients admitted to both medical and surgical wards and found out the following results:

Table 1. Incidence of phlebitis in the study patients (non-related factors)

Parameter	Sample size	Phlebitis (n)	Incidence (%)	OR (Odds ratio)	95% CI for OR
Age					
<60 year	169	47	27.8	1.18	0.79-
≥60 years	131	31	23.7		1.74
Trauma					
Yes	58	19	32.8	1.34	0.87-
No	242	59	24.4		2.07
Size of catheters					
20 G	109	30	27.5	1.11	0.75-
18 G	190	47	24.7		1.65

Table 2. Incidence of phlebitis in the study patients (related factors)

Parameter	Sample size	Phlebitis (n)	Incidence (%)	OR (Odds ratio)	95% CI for OR
Gender					
Female	155	48	31.0	1.50	1.01-
Male	145	30	20.7		2.22
Diabetes mellitus					
Yes	111	64	57.7	7.78	4.59-
No	189	14	7.4		13.21
Burns					
Yes	3	3	100	3.96	3.26-
No	297	75	25.3		4.82
Infectious disease					
Yes	67	50	74.6	6.21	4.27-
No	233	28	12.0		9.03
Site of catheters					
Lower ext	13	10	76.9	3.25	2.26-
Upper ext	287	68	23.7		4.67
Type of catheter insertion					
Urgent	140	50	35.7	2.04	1.36-
Non-urgent	160	28	17.5		3.05

How to detect and to assess the presence of infusion phlebitis?

Visual infusion phlebitis score has been developed by Andrew Jackson ⁽⁸⁾ as follows:

V.I.P. Score (Visual infusion phlebitis score)

	I.V. site appears healthy	0	No sign of phlebitis ■ OBSERVE CANNULA
	One of the following is evident : Slight pain near the i.v. site or slight redness near the i.v. site	1	Possible first sign of phlebitis ■ OBSERVE CANNULA
	Two of the following are evident: ● Pale near i.v. site ● Erythema ● Swelling	2	Early stage of phlebitis ■ RESITE CANNULA
	All of the following are evident: ● Pain along path of cannula ● Erythema ● Induration	3	Medium stage of phlebitis ■ RESITE CANNULA ■ CONSIDER TREATMENT
	All of the following are evident & extensive: ● Pain along path of cannula ● Erythema ● Induration ● Palpable venous cord	4	Advanced stage of phlebitis or start of thrombophlebitis ■ RESITE CANNULA ■ CONSIDER TREATMENT
	All of the following are evident & extensive: ● Pain along path of cannula ● Erythema ● Induration ● Palpable venous cord ● pyrexia	5	Advanced stage of thrombophlebitis ■ INITIATE TREATMENT ■ RESITE CANNULA

How to prevent and to treat infusion-related phlebitis?

In addition to the above simple guideline, the following should be considered

1. Prevent bacterial phlebitis:

A detailed description regarding the guideline of for preventing catheter related infections can be download from www.pediatrics.org.⁽⁹⁾ focusing on the hand hygiene, aseptic technique, iv. Site care, and cutaneous antisepsis. Although a 2% chlorhexidine-based preparation is preferred, tincture of iodine, an iodophor, or 70% alcohol can be used.

2. Keep alert and do not underestimate aseptic technique.

Even, Stopcocks (used for injection of medications, administration of IV infusions, and collection of blood samples) represent a potential portal of entry for microorganisms into vascular access catheters and IV fluids. Stopcock contamination is common, occurring in 45% and 50% in the majority of series

3. Rotating cannula

May et al (2005)⁽¹⁰⁾ reported the results of 4 techniques of administering PPN, by which rotating cannula daily to contralateral arm is associated with zero incidence of phlebitis in group of 15 patients. However, in a randomized controlled trial published recently by Webster et al ⁽⁶⁾ it was concluded that catheters may be safely left in place for longer than 72 hours if no contraindications are present. The Centers for Disease Control and Prevention advocate replacing catheters every 72-96 hours to limit the potential for infection, but the recommendation is based on scant evidence ⁽⁹⁾

4. Aseptic dressing

The aseptic dressing method is recommended to be prevent infusion phlebitis. sterile gauze dressing which was changed every 24 hours ⁽¹¹⁾.

5. Rate of administration

Experts are commonly unanimous that the slower the rate of infusion of hypertonic solutions the lower the risk of phlebitis. However, a different paradigm exists for infusion of high osmolarity drugs. Osmolalities of the infusion can approach 1000 mOsm/L if the duration of the infusion is only several hours.⁽¹²⁾ Duration of infusion should be less than three hours to reduce the time the irritating mixture contacts the vein wall. This requires high (150 – 330 mL/hour) infusion rates. The largest vein, and smallest and shortest catheter possible to achieve the infusion rate desired should be used, with in-line filtration of at least 0.45mm. The cannula should be removed at the first sign of pain or redness. This relatively high speed of administration is rather relevant for iv drug administration, NOT for maintenance fluid therapy or parenteral nutrition support.

6. Titratable acidity

The titratable acidity of infusion solutions has never been taken into account in infusion phlebitis. Titratable acidity measures the amount of alkali required to neutralize the pH of infusion solutions. The phlebitic potential of infusion solutions cannot be estimated by pH or titratable acidity alone. Even at pH 4.0, a commercial 10% glucose solution rarely caused any change because of its very low titratable acidity (0.16 mEq/L).⁽¹³⁾ Thus, the lower titratable acidity of any infusion solutions the lower the risk of phlebitis

7. Heparin & hydrocortisone

Heparin sodium, when added to infusion fluids to a final concentration of 1 unit/mL, diminishes local intravenous catheter-related problems and extends the catheter's life^(14,15). The risk of phlebitis associated with the infusion of certain fluids (e.g., potassium chloride, lidocaine, and antimicrobials) also may be reduced by the use of certain IV additives, such as hydrocortisone. In trials of patients in coronary care units, heparin or hydrocortisone significantly reduced the incidence of phlebitis in veins infused with lidocaine, potassium chloride, or antimicrobials⁽¹⁶⁾. In two other randomized trials, heparin alone or in combination with hydrocortisone has reduced phlebitis, but the use of heparin in lipid-containing solutions may be associated with the formation of calcium precipitates.

8. In-line filters

In-line filters may reduce the incidence of infusion-related phlebitis, but there are no data to support their efficacy in preventing infections associated with intravascular devices and infusion systems⁽¹⁶⁾.

9. Cyclic Infusion

Recently, Kuwahara et al⁽¹⁷⁾ reported their observation that cyclic infusion is effective in reducing phlebitis caused by peripheral parenteral nutrition solution. This

study has encouraged a new trend in Japan of giving cyclic infusion on daytime only instead of 24 hr continuous administration.

CONCLUSION

Phlebitis is still a common problem in fluid therapy, when administering intravenous drugs, maintenance fluid therapy as well as parenteral nutrition. Multiple causative and predisposing factors include old age, size of catheter, diabetes mellitus, infectious diseases, hyperosmolarity and pH, titrable acidity of infusion solution and poor aseptic techniques, etc. Clinicians should consider the multifactorial causes and implement a strict monitoring to prevent and treat properly to avoid serious complications.

References:

- 1) Nassaji-Zavareh M, Ghorbani.R. Peripheral intravenous catheter- related phlebitis and related risk factors. Singapore Med J 2007; 48 (8) : 733
- 2) Falchuk KH, Peterson L, and McNeil BJ Microparticulate-induced phlebitis. Its prevention by in-line filtration. NEJM. Vol 312:78-82. Jan 10, 1985
- 3) Pose-Reino A, J. M. Taboada-Cotón A.J.M, ; Alvarez D, Suarez J., Valdés L. Infusion Phlebitis in Patients in a General Internal Medicine Service. (Chest. 2000;117:1822-1823.)© 2000 American College of Chest Physicians
- 4) Nordenström J, Jeppsson B, Lovén, Larsson J. Peripheral parenteral nutrition: Effect of a standardized compounded mixture on infusion phlebitis. British Journal of Surgery Volume 78 Issue 11, Pages 1391 - 1394. 2005
- 5) Manuel Monreal et al. Infusion Phlebitis in Patients With Acute Pneumonia* A Prospective Study (Chest. 1999;115:1576-1580.)© 1999 American College of Chest Physicians
- 6) Joan Webster et al. Routine care of peripheral intravenous catheters versus clinically indicated replacement: randomised controlled trial. BMJ 2008;337:a339
- 7) Terry Judy. Intravenous therapy. Clinical Principles and Practice. WB Saunders Company 1995. pp 423-426

- 8) Andrew Jackson, Consultant Nurse Intravenous Therapy and Care, Rotherham General Hospitals, NHS Trust
- 9) Naomi P.O'Grady. Guidelines for the Prevention of Intravascular Catheter-Related Infections. American Academy of Pediatrics
- 10) May J, et al. Prospective study of the aetiology of infusion phlebitis and line failure during peripheral parenteral nutrition British Journal of Surgery Volume 83 Issue 8, Pages 1091 – 1094 Published Online: 6 Dec 2005
- 11) Lee KE, Yom YH, Oh JS, Kim KM. The effect of the aseptic dressing method on infusion phlebitis. J Korean Acad Fundam Nurs. 2000 Aug;7(2):177-191. Korean
- 12) Ian D. Bier. Peripheral Intravenous Nutrition Therapy: Outpatient, Office-Based Administration. Altern Med Rev 2000;5(4):347-354
- 13) Kuwahara T, Asanami S, Tamura T, Kubo S. Experimental infusion phlebitis: importance of titratable acidity on phlebitic potential of infusion solution. Clin Nutr. 1996 Jun;15(3):129-32
- 14) JA Nieto-Rodriguez, MA Garcia-Martin, MD Barreda-Hernandez, MJ Hervas, and O Cano-Real Heparin and infusion phlebitis: a prospective study The Annals of Pharmacotherapy: Vol. 26, No. 10, pp. 1211-1214. © 1992 Harvey Whitney Books Company.
- 15) Randolph AG et al. Benefit of heparin in peripheral venous and arterial catheters: systematic review and meta-analysis of randomised controlled trials. BMJ 1998;316:969-975 (28 March)
- 16) Michele L. Pearson, MD; The Hospital Infection Control Practices Advisory Committee GUIDELINE FOR PREVENTION OF INTRAVASCULAR DEVICE-RELATED INFECTIONS. AJIC Am J Infect Control 1996;24:262-93
- 17) Kuwahara et al. Cyclic infusion is effective in reducing phlebitis caused by peripheral parenteral nutrition solutions: An experimental study in rabbitse-SPEN, The European e-Journal of Clinical Nutrition and Metabolism Volume 4, Issue 6 , Pages e344-e347, December 2009

EXTRAVASATION & INFILTRATION

Iyan Darmawan

Within the context of infusion therapy extravasation literally means the escape of infusion solution from blood vessel into the surrounding tissue. However, more detailed exploration clarifies the following definition:

- *Extravasation* - The inadvertent administration of a vesicant solution or medication into surrounding tissue.
- *Infiltration* - The inadvertent administration of a nonvesicant solution/medication into a surrounding tissue.
- *Irritant* - Agents that have the potential to irritate tissue if extravasation occurs.
- *Nonvesicant* - A solution/medication, which does not cause blistering when infiltrated.
- *Vesicant* - A solution or medication that causes a blistering process when inadvertently administered into the surrounding tissue.

The distinction between infiltration and extravasation is important because the management strategy for each situation is different from each other.

Common signs of infiltration are:^{1,2,3}

- Edema at the insertion site
- Taut or stretched skin
- Blanching or coolness of the skin
- Slowing or stopping of the infusion
- Leaking of I.V. fluid out of the insertion site.

Tissue damage

Vesicants, by definition, have the potential to cause tissue damage upon extravasation from the vein. Like the initial symptoms, the extent of tissue damage can

vary greatly between different treatment regimens and patients.

Tissue destruction caused by leakage of vesicants into surrounding tissue may be progressive in nature, and may happen quite slowly with little pain. Induration or ulcer formation is by no means an immediate phenomenon – as it takes time to develop. In general, tissue damage begins with the appearance of inflammation and blisters at or near the site of injection.

Depending on the drug and other factors, this can then progress to ulceration, and then in some cases may progress to necrosis of the local tissue. Necrosis can occasionally be so severe that function in the affected area cannot be recovered and surgery is required.

Vein selection in peripheral administration

The choice of vein for the infusion is an equally important consideration for the prevention of extravasation. Finding the largest, softest and most pliable vein is the best choice to avoid complications. Some general guidelines include:

1. Try to use the forearm, not the back of the hand
2. Avoid small and fragile veins
3. Avoid insertion on limbs with lymphoedema or with neurological weakness
4. Avoid veins next to joints, tendons, nerves or arteries
5. Avoid the antecubital fossa (area near the elbow)

Early Management of extravasation.¹

Step 1 Stop the infusion immediately. DO NOT remove the cannula at this point.



Step 2 Disconnect the infusion (not the cannula/needle).



Step 3 Leave the cannula/needle in place and try to aspirate as much of the drug as possible from the cannula with a 10 mL syringe. Avoid applying direct manual pressure to suspected extravasation site.



Step 4 Mark the affected area and take digital images of the site.



Step 5 Remove the cannula/ needle.

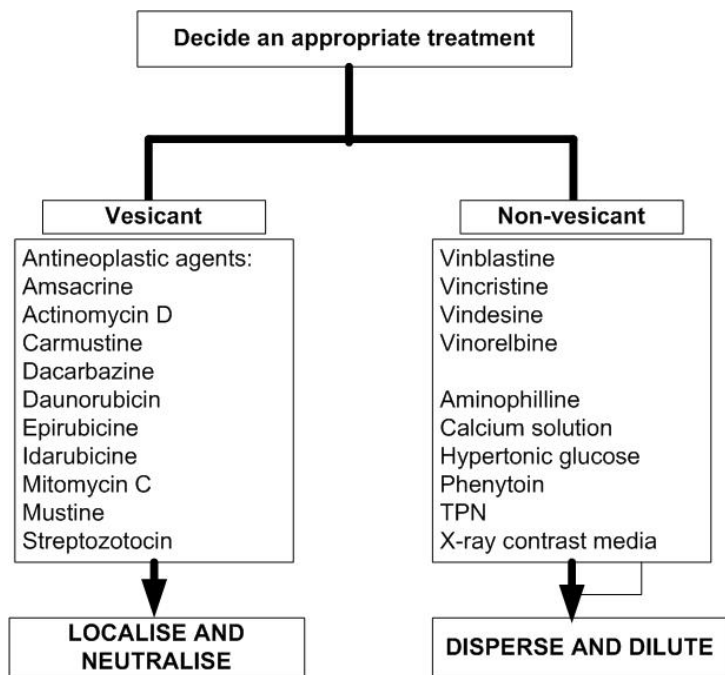


Step 6 Collect the extravasation kit (if available), notify the physician on service and seek advice from the chemotherapy team or Senior Medical Staff.



Step 7 Administer pain relief if required. Complete required documentation.

Further Management

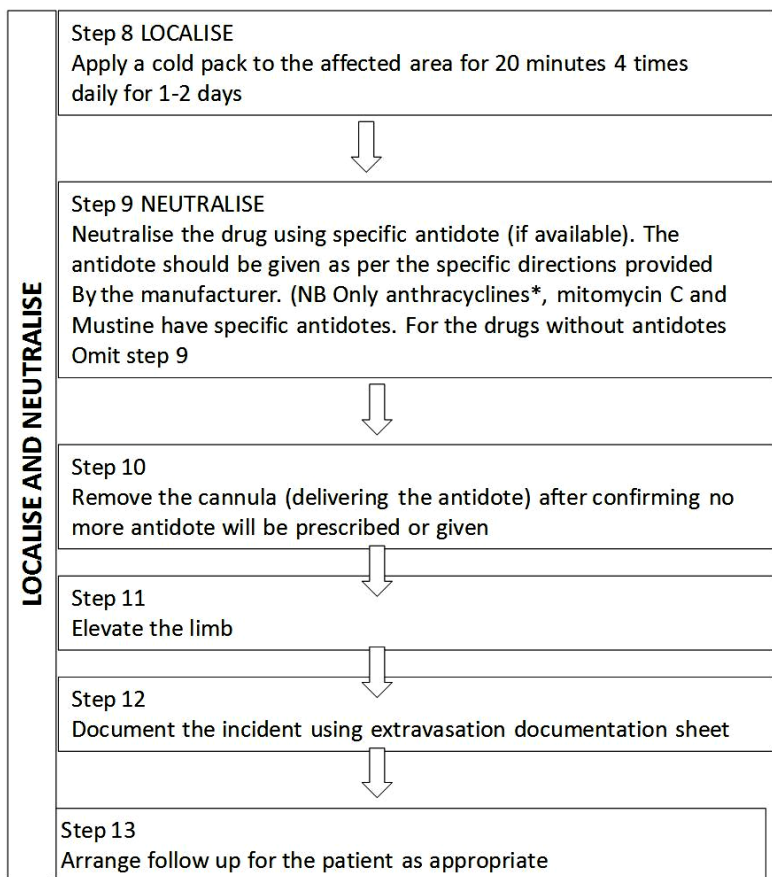


If the drug is a non-vesicant, application of a simple cold compress and elevation of the limb may be sufficient to limit the swelling etc. In contrast, the extravasation of a vesicant requires several steps and differs for the various classes of drug. There are two broad approaches to limiting the damage caused by extravasation: localisation and neutralisation; or dispersion and dilution.

Localise and neutralise strategy

■ Use cold compresses to limit the spread of infusate. It used to be thought that cold limited spread through vasoconstriction. In animal models, it appears that cold prevents spread by a mechanism other than vasoconstriction suggested to be decreased cellular uptake of drug at lower temperatures

- Consider using antidotes to counteract vesicant actions.



Disperse and dilute strategy

- Appropriate for the extravasation of vinca alkaloids
- Use warm compresses to prompt vasodilation and encourage blood flow in the tissues, thereby spreading the infusate around
- Consider using hyaluronidase to dilute infusate

DILUTE AND DISPERSE	Step 8 DISPERSE Apply a warm compress to the affected area for 20 minutes 4 times daily for 1-2 days
	↓
	Step 9 DILUTE Give several subcutaneous injections of 150-1500 IU of hyaluronidase diluted in 1 mL sterile water around the extravasated Area to dilute the infusate
	↓
	Step 12 Document the incident using extravasation documentation sheet
	↓
	Step 13 Arrange follow up for the patient as appropriate

CONCLUSION

Recognition and differentiation between infiltration and extravasation should be considered as an important aspect in monitoring infusion therapy as well as administration of parenteral drugs. In the event of infiltration the appropriate management is generally “dilute and disperse” whereas in extravasation (of vesicant substances) the “localise and neutralise” strategy should be adopted.

References:

1. Wengström Y, Margulies A. European Oncology Nursing Society extravasation guidelines. *European Journal of Oncology Nursing* (2008) 12, 357–361
2. Schulmeister L. Extravasation Management. *Seminars in Oncology Nursing*, Vol 23, No 3 (August), 2007: pp 184–190
3. Wiegand R, Brown J. Hyaluronidase for the management of dextrose extravasation *American Journal of Emergency Medicine* (2010) 81, 257.e1–257.e

WHAT IS PROTEIN-SPARING EFFECT?

Iyan Darmawan

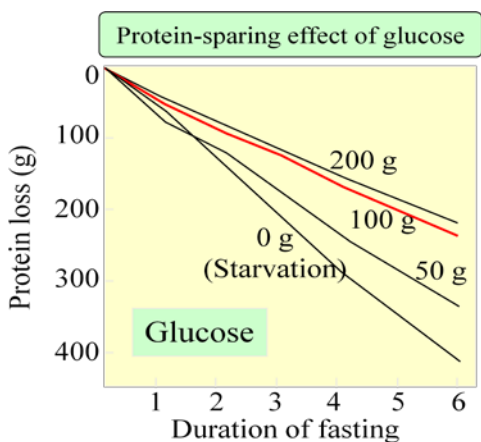
Protein sparing is the process by which the body derives energy from sources other than protein. Such sources can include fatty tissues, dietary fats and carbohydrates. Protein sparing conserves muscle tissue. The balance between digestible protein (DP) and digestible energy (DE) in the diet is a key factor. Decreasing dietary DP/DE ratio results in an increase of protein conservation. The amino acids are not catabolized for energy, and are conserved in the body in a greater ratio.

Leucine, a branched-chain amino acid has been recently known also to have protein-sparing effect.^{1,2}

The amount of protein used in the body is influenced by the percentage that is digestible by the body, and the total quantity of protein fed to the body. Bodybuilding and other strength training promotes the utilization and conservation of protein's amino acids in the body. Using alternate energy sources lessens the amount of amino acids that will be metabolized for energy. Non carbohydrate sources such as alanine, acetate, lactate, glycerol, branched-chain ketoacids are also known to exert protein-sparing effects.

In clinical nutrition, the concept of protein-sparing effect was introduced by Gamble.³

During starvation in a 70 kg man, approximately 80 g/day, or approximately 400 g for six days, of proteins was lost due to the catabolism of body proteins. This is equivalent to approximately 2 kg of muscle. After glucose administration, the protein catabolism was inhibited. The protein loss at a glucose dose of 100 g/day was approximately 40 g/day or approximately 200 g for six days. This means, glucose administration inhibited the protein loss to approximately 50% of that during starvation.



When glucose was administered at 200 g, The degree of protein catabolism was similar to that at 100 g. This indicates that administration of glucose, i.e., an energy source, alone cannot fully inhibit the catabolism of body proteins.

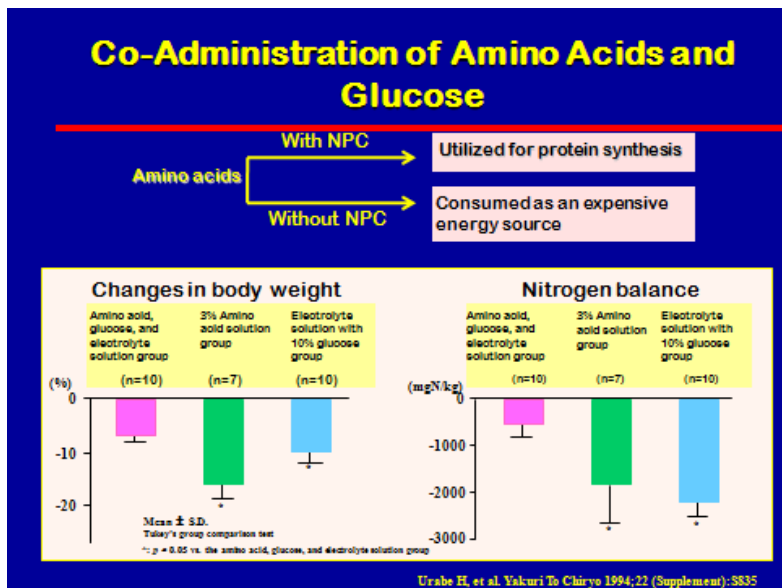
Approximately 40 g of proteins at minimum is necessary as a daily average intake to maintenance N-balances under no stress conditions. For this purpose, 100 g/day of glucose is required at minimum.

Under stress conditions such as surgery, the energy demand is increased and protein catabolism is further enhanced. It becomes more difficult to inhibit protein catabolism by glucose administration alone.

In this case, supplementation of not only energy sources (carbohydrates and fats) but also amino acids that are used for protein synthesis is important to improve N-balance and protein metabolism and then inhibit the catabolism of body proteins.

A group of japanese investigators showed that combination of amino acids, glucose and electrolytes is more effective than exclusive amino acids or electrolyte

plus 10% glucose solution in minimizing weight loss and negative nitrogen balance ⁴



Intraoperative protein sparing with glucose

Schricker et al examined the hypothesis that glucose infusion inhibits amino acid oxidation during colorectal surgery⁵. They randomly allocated 14 patients to receive intravenous glucose at $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (glucose group) starting with the surgical incision or an equivalent amount of normal saline 0.9% (control group). The primary endpoint was whole body leucine oxidation; secondary endpoints were leucine rate of appearance and nonoxidative leucine disposal as determined by a stable isotope tracer technique. Circulating concentrations of glucose, lactate, insulin, glucagon, and cortisol were measured before and after 2 h of surgery. Leucine rate of appearance, an estimate of protein breakdown, and nonoxidative leucine disposal, an estimate of protein synthesis, decreased in both groups during surgery ($P < 0.05$). Leucine oxidation intraoperatively decreased from

13 ± 3 to $4 \pm 3 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ in the glucose group ($P < 0.05$ vs. control group) whereas it remained unchanged in the control group.. The provision of small amounts of glucose was associated with a decrease in amino acid oxidation during colorectal surgery.

Parenteral nutrition and protein sparing after surgery

Although capable of inducing an anabolic state after surgery, parenteral nutrition, including glucose, leads to hyperglycemia. Even moderate increases in blood glucose are associated with poor surgical outcome. Thomas Schricker et al examined the hypothesis that amino acids, in the absence of glucose supply, spare protein while preventing hyperglycemia.⁶ In this prospective study, 14 patients with colonic cancer were randomly assigned to undergo a 6-hour stable isotope infusion study (3 hours of fasting followed by 3-hour infusions of 10 % amino acids 10% at $0.02 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, with or without glucose at $4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) on the second day after colorectal surgery.

Protein breakdown, protein oxidation, protein balance, and glucose production were assessed by stable isotope tracer kinetics using leucine and glucose isotops. Circulating concentrations of glucose, cortisol, insulin, and glucagon were determined. The administration of amino acids increased protein balance from $-16 \pm 4 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ in the fasted state to $16 \pm 3 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. Combined infusion of amino acids and glucose increased protein balance from -17 ± 7 to $7 \pm 5 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. The increase in protein balance during nutrition was comparable in the 2 groups ($P = .07$). Combined administration of amino acids and glucose decreased endogenous glucose production ($P = .001$) and stimulated insulin secretion ($P = .001$) to a greater extent than the administration of amino acids alone.

Is Protein-Sparing Effect Considered in Formulation of Maintenance Solution ?

New generation dual-chamber maintenance solutions like Aminofluid® contain combination of glucose and amino acids to prevent consumption of amino acids as energy source and thus have favourable profile on nitrogen balance. In addition, the content of electrolytes is necessary for water and electrolyte homeostasis, while microminerals and zinc facilitate cellular metabolism.

References:

1. Shimomura Y et al. Nutraceutical Effects of Branched-Chain Amino Acids on Skeletal Muscle. American Society for Nutrition J. Nutr. 136:529S-532S, February 2006
2. Mitchell JC, Evenson AR, Tawa NE: Leucine inhibits proteolysis by the mTOR kinase signaling pathway in skeletal muscle. J Surg Res 2004, 121:311.
3. Brody T. Nutritional Biochemistry, Second Edition, p 454
4. Urabe H, et al. Yakuri To Chiryo 1994;22 (Supplement):S835
5. Schricker T, Lattermann R, and Carli F Intraoperative protein sparing with glucose J Appl Physiol 99: 898–901, 2005
6. (Schricker T Parenteral nutrition and protein sparing after surgery: do we need glucose? Original Research Article Metabolism, Volume 56, Issue 8, August 2007, Pages 1044-1050,)

BRANCHED-CHAIN AMINO ACIDS ENHANCE THE COGNITIVE RECOVERY OF PATIENTS WITH SEVERE TRAUMATIC BRAIN INJURY

Iyan Darmawan

BRANCHED-CHAIN AMINO ACIDS (BCAAs) (leucine, valine, isoleucine) are essential amino acids for humans, so they must be sourced from the diet. BCAAs account for approximately 35% of the essential amino acids and 14% of the total amount of amino acids in skeletal muscle¹. After a meal, BCAAs constitute at least 50% of the amino acid uptake by skeletal muscle². The mean requirement and population-safe level (upper limit of 95% confidence interval) of the total BCAA were 144 and 210 mg/(kg/ d), respectively.³ It is well documented that BCAAs may favorably influence protein metabolism by inhibiting muscle protein breakdown and promoting muscle and hepatic protein synthesis⁴. It has been reported that supplying BCAAs to injured and septic animals and to stressed patients has beneficial effects⁵.

Parenterally administered BCAAs are used clinically in nutritional support for postoperative, traumatized, and septic patients, and the oral use of BCAAs suppresses whole-body proteolysis in tissues other than skeletal muscle in healthy men. Beside these strictly nutritional aspects of BCAAs, numerous studies suggest that these amino acids may also have a notable effect on cognitive functions⁶. In clinical settings, orally administered or parenterally infused BCAAs improved mental status, flapping, orientation, speech, and writing in patients with cirrhosis and chronic hepatic encephalopathy⁷. Patients with Alzheimer's dementia had a significantly lower ratio of cerebrospinal fluid to plasma levels of valine (and other amino acids tested) than did control subjects, and significant correlations were found between memory and cognitive functions and cerebrospinal fluid–valine concentration. It is well documented that BCAAs, particularly leucine, are essential for the regulation of insulin production by pancreatic beta cells⁸. When

leucine was ingested with glucose, it attenuated the serum glucose response and strongly stimulated additional insulin secretion⁹

Early studies found that leucine not only stimulates insulin release but also is the sole indispensable amino acid capable of inducing insulin secretion, even in the absence of glucose. Therefore, it goes without saying that BCAAs are most studied amino acids both experimentally and clinically. Recently, BCAAs had been reported to improve central fatigue and anorexia by competitively blocking the influx of tryptophan (precursor of serotonin) into the CNS^{10,11,12}. Wu et al found the beneficial effect of BCAAs in relieving postoperative fatigue¹³.

Result of study in posttraumatic brain injury¹⁴

BCAA Supplementation and Cognitive Function: At present, we can only speculate about the mechanism underlying the improved cognition associated with BCAAs. However, some acceptable mechanisms include a direct action of the BCAAs on brain function by providing substrates and an indirect action by increasing brain insulin availability.

It is reasonable to believe that normalization of plasma concentrations of BCAAs may lead to increased BCAA provision to the brain. These amino acids may be used to produce energy and synthesize proteins in the central nervous system (CNS). Given that they are amino acids, BCAAs can enter the energy-producing oxidative pathway of the Krebs cycle so that higher amounts of adenosine 5'-triphosphate (ATP) can be formed. The finding that processed amino acids in the Krebs cycle make a very large contribution to ¹⁴CO₂ production of brain cells supports this BCAA supplementation mechanism of effect. An increase in brain ATP availability in TBI may represent an important factor, contrasting the cascade of biochemical alterations

caused by the injury. For instance, in severe brain injury, ATP depletion is responsible for alterations in ion pumps, which bring about a failure of cellular sodium, potassium, and calcium homeostasis. The loss of ion homeostasis contributes to the death of neurons in TBI. Therefore, BCAA supplementation might protect and restore the function of those neurons that are still viable although metabolically altered.

The BCAAs, particularly leucine, play an important role in mediating amino acid-regulated steps of protein synthesis. To get an idea of the importance of active protein synthesis for the brain structures of TBI patients, it is sufficient to mention that *de novo* protein synthesis is essential for brain tissue repair, sprouting, and circuitry remodeling. BCAAs may also favor the recovery of cognition indirectly by an insulin-mediated action. This hypothesis is highly plausible, both because BCAAs induce insulin secretion and release and because this hormone crosses the blood-brain barrier, exerting profound effects on the CNS.

Roberto Aquilani et al investigated whether supplementation with branched-chain amino acids (BCAAs) in patients with severe traumatic brain injury (TBI) improves recovery of cognition and influences plasma concentrations of tyrosine and tryptophan, which are precursors of, respectively, catecholamine and serotonin neurotransmitters in the brain.

They randomly assigned forty patients with TBI to 15 days of intravenous BCAA supplementation (19.6g/d) (n= 20) or an isonitrogenous placebo (n=20).

Participants were Forty men (mean age, 32± 15y) with TBI and 20 healthy subjects (controls) matched for age, sex, and sedentary lifestyle.

Disability Rating Scale (DRS) and plasma concentrations of BCAAs, tyrosine, and tryptophan were used as Main Outcome Measures:

Results: Fifteen days after admission to the rehabilitation department, the DRS score had improved significantly in

both the placebo group ($P < .05$ vs baseline) and in the BCAA-supplemented group ($P < .01$ vs baseline). The difference between the 2 groups was significant ($P < .004$). Plasma tyrosine concentration improved in the group given BCAA supplementation, and tryptophan concentration increased in patients receiving placebo. The authors concluded that Supplemental BCAAs enhance the retrieval of DRS without causing negative effects on tyrosine and tryptophan concentration.

References:

1. Ruderman NB, Schmahl FW, Goodman MN. Regulation of alanine formation and release in rat muscle in vivo: effect of starvation and diabetes. *Am J Physiol* 1977;233:109-14.
2. Rodwell VW. Catabolism of amino acid nitrogen. In: Murray RK, Granner DK, Mayes PA, editors. *Harper's biochemistry*. Norwalk: Appleton & Lange; 1988. p 271-80
3. Riazzi, R., Wykes, L. J., Ball, R. O. & Pencharz, P. B. (2003) The total branched-chain amino acid requirement in young healthy adult men determined by indicator amino acid oxidation by use of L-[1-13C] phenylalanine. *J. Nutr.* 133:1383-1389
4. Zanchi NE et al Potential antiproteolytic effects of L-leucine: observations of in vitro and in vivo studies. *Nutrition & Metabolism* 2008, 5:20
5. Sobotkaa L abd Soetersa PB. Basics in clinical nutrition: Metabolic response to injury and sepsis e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism Volume 4, Issue 1, February 2009
6. Yamamoto T. Effect on neurocognition and mental fatigue after BCAA administrations. Abstracts / Neuroscience Research 58S (2007) S1–S244
7. Takahashi Y. et al. A multicenter clinical study of a specially-formulated amino acid injection (GO-80) in hepatic encephalopathy (II). *J New Remedies and Clinics.* 1982;31:186-244
8. Yoshizawa F. Regulation of protein synthesis by branched-chain amino acids in vivo Biochemical and Biophysical Research Communications Volume 313, Issue 2, 9 January 2004, Pages 417-422

9. Kalogeropoulou D. Leucine,when ingested with glucose, synergistically stimulates insulin secretion and lowers blood glucose. *Metabolism* Volume 57, Issue 12, December 2008, Pages 1747-1752
10. Cangiano C et al. Effects of Administration of Oral Branched-Chain Amino Acids on Anorexia and Caloric Intake in Cancer Patients*Journal of the National Cancer Institute*, Vol. 88, No. 8, April 17, 1996
11. Yamamoto T. Diminished central fatigue by inhibition of the L-system transporter for the uptake of tryptophan. *Brain Research Bulletin*, Vol. 52, No. 1, pp. 35–38, 2000
12. James McGuire J et al, Biochemical markers for post-operative fatigue after major surgery *Brain Research Bulletin*, Volume 60, Issues 1-2, 15 April 2003, Pages 125-130
13. Wu D et al: Effect of branched chain amino acid enriched formula on postoperative fatigue and nutritional status after digestive surgery; *Zhonghua Wei Chang Wai Ke Za Zhi*. 2005 May; 8(3): 226-8
14. Aquilani R et al: Branched-chain amino acids enhance the cognitive recovery of patients with severe traumatic brain injury; *Arch Phys Med Rehabil*. 2005 Sep; 86(9): 1729-35

INSULIN RESISTANCE

Iyan Darmawan

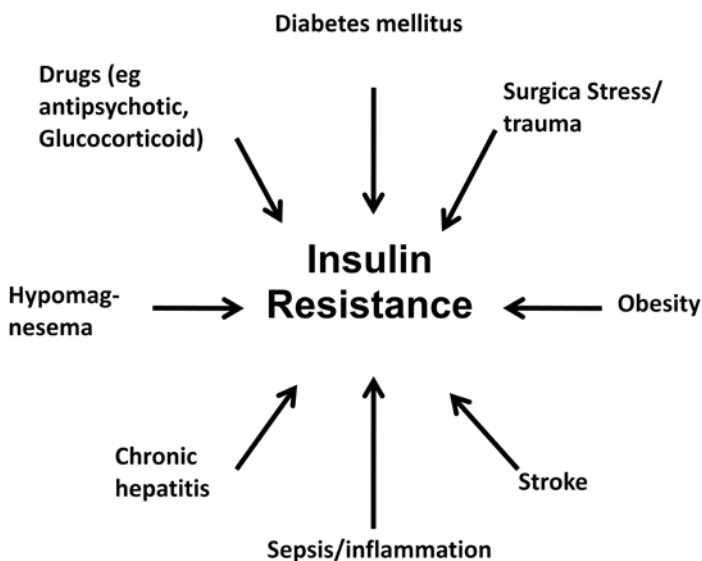
Introduction

What is it?

Insulin resistance (IR) is the condition in which normal amounts of insulin are inadequate to produce a normal insulin response from fat, muscle and liver cells. Insulin resistance in fat cells reduces the effects of insulin and results in elevated hydrolysis of stored triglycerides in the absence of measures which either increase insulin sensitivity or which provide additional insulin. Increased mobilization of stored lipids in these cells elevates free fatty acids in the blood plasma. Insulin resistance in muscle cells reduces glucose uptake (and so local storage of glucose as glycogen), whereas insulin resistance in liver cells results in impaired glycogen synthesis and a failure to suppress glucose production. Elevated blood fatty-acid concentrations (associated with insulin resistance and diabetes mellitus Type 2), reduced muscle glucose uptake, and increased liver glucose production all contribute to elevated blood glucose concentration. Unlike type 1 diabetes mellitus, insulin resistance is generally "post-receptor", meaning it is a problem with the cells that respond to insulin rather than a problem with the production of insulin. High plasma levels of insulin and glucose due to insulin resistance are believed to be the origin of metabolic syndrome and type 2 diabetes, including its complications.

What cause it?

There are several conditions causing insulin resistance.



Pathophysiology

In a person with normal metabolism, insulin is released from the beta (β) cells of the Islets of Langerhans located in the pancreas after eating ("postprandial"), and it signals insulin-sensitive tissues in the body (e.g., muscle, adipose) to absorb glucose. This lowers blood glucose levels. The beta cells reduce their insulin output as blood glucose levels fall, with the result that blood glucose is maintained at approximately 5 mmol/L (mM) (90 mg/dL). In an insulin-resistant person, normal levels of insulin do not have the same effect on muscle and adipose cells, with the result that glucose levels stay higher than normal. To compensate for this, the pancreas in an insulin-resistant individual is stimulated to release more insulin. The elevated insulin levels have additional effects (see insulin) which cause further biological effects throughout the body.

The most common type of insulin resistance is associated with a collection of symptoms known as metabolic syndrome. Insulin resistance can progress to

full Type 2 diabetes mellitus (T2DM). This is often seen when hyperglycemia develops after a meal, when pancreatic β -cells are unable to produce sufficient insulin to maintain normal blood sugar levels (euglycemia). The inability of the β -cells to produce sufficient insulin in a condition of hyperglycemia is what characterizes the transition from insulin resistance to Type 2 diabetes mellitus. ^[1]

Various disease states make the body tissues more resistant to the actions of insulin. Examples include infection (mediated by the cytokine TNF α) and acidosis. Recent research is investigating the roles of adipokines (the cytokines produced by adipose tissue) in insulin resistance. Certain drugs may also be associated with insulin resistance (e.g., glucocorticoids).

Insulin itself can lead to insulin resistance; every time a cell is exposed to insulin, the production of GLUT4 (type four glucose receptors) on the cell's membrane is decreased. ^[2] This leads to a greater need for insulin, which again leads to fewer glucose receptors. Exercise reverses this process in muscle tissue, ^[3] but if left unchecked, it can spiral into insulin resistance.

Elevated blood levels of glucose — regardless of cause — leads to increased glycation of proteins with changes (only a few of which are understood in any detail) in protein function throughout the body.

Insulin resistance is often found in people with visceral adiposity (i.e., a high degree of fatty tissue underneath the abdominal muscle wall - as distinct from subcutaneous adiposity or fat between the skin and the muscle wall, especially elsewhere on the body, such as hips or thighs), hypertension, hyperglycemia and dyslipidemia involving elevated triglycerides, small dense low-density lipoprotein (sdLDL) particles, and decreased HDL cholesterol levels. With respect to visceral adiposity, a great deal of evidence suggests two

strong links with insulin resistance. First, unlike subcutaneous adipose tissue, visceral adipose cells produce significant amounts of proinflammatory cytokines such as tumor necrosis factor- α (TNF- α), and Interleukins-1 and -6, etc. In numerous experimental models, these proinflammatory cytokines profoundly disrupt normal insulin action in fat and muscle cells, and may be a major factor in causing the whole-body insulin resistance observed in patients with visceral adiposity. A great deal of attention into the production of proinflammatory cytokines has focused on the IKK-beta/NF-kappa-B pathway, a protein network that enhances transcription of cytokine genes. Second, visceral adiposity is related to an accumulation of fat in the liver, a condition known as nonalcoholic fatty liver disease (NAFLD). The result of NAFLD is an excessive release of free fatty acids into the bloodstream (due to increased lipolysis), and an increase in hepatic glucose production, both of which have the effect of exacerbating peripheral insulin resistance and increasing the likelihood of Type 2 diabetes mellitus. ^[4]

Insulin resistance is also often associated with a hypercoagulable state (impaired fibrinolysis) and increased inflammatory cytokine levels.

Insulin resistance is also occasionally found in patients who use insulin. In this case, the production of antibodies against insulin leads to lower-than-expected glucose level reductions (glycemia) after a specific dose of insulin. With the development of human insulin and analogues in the 1980s and the decline in the use of animal insulins (e.g., pork, beef), this type of insulin resistance has become uncommon.

Magnesium (Mg) is present in living cells and its plasma concentration is remarkably constant in healthy subjects. Plasma and intracellular Mg concentrations are tightly regulated by several factors. Among them, insulin seems to be one of the most important. In vitro and in vivo

studies have demonstrated that insulin may modulate the shift of Mg from extracellular to intracellular space. Intracellular Mg concentration has also been shown to be effective in modulating insulin action (mainly oxidative glucose metabolism), offset calcium-related excitation-contraction coupling, and decrease smooth cell responsiveness to depolarizing stimuli. Poor intracellular Mg concentrations, as found in Type 2 diabetes mellitus and in hypertensive patients, may result in a defective tyrosine-kinase activity at the insulin receptor level and exaggerated intracellular calcium concentration. Both events are responsible for the impairment in insulin action and a worsening of insulin resistance in noninsulin-dependent diabetic and hypertensive patients. By contrast, in T2DM patients daily Mg administration, restoring a more appropriate intracellular Mg concentration, contributes to improve insulin-mediated glucose uptake. The benefits deriving from daily Mg supplementation in T2DM patients are further supported by epidemiological studies showing that high daily Mg intake are predictive of a lower incidence of T2DM. ^[5,6]

How to detect/ measure insulin resistance?

Serum insulin concentration is seldom measured in clinical practice. For research purposes, there are various methods of measurement. Among others, the simplest ways of detecting insulin resistance are as follows ^[7] :

1. HOMA (homeostatic model assessment), using formula:

$$\frac{Io \times Go}{405}$$

where

1. Io =fasting insulin level (μ U/ml)
2. Go=fasting glucose level (mg/dl)
3. Normal value 100%

HOMA2 Calculator

Fasting Values

Plasma glucose : 120 ☐ mmol/l ☒ mg/dl

Insulin 18 ☐ pmol/l ☒ μ U/ml

%B : 97.8 %S : 40.7 = IR : 2.5

Calculate Copy Print

About Preferences Exit

2. G/I ratio. Ratio < 4.5 indicates the presence of IR
3. Fasting serum insulin (I_0). Normal upper limit of fasting serum insulin is 60 pmol/L or 8.6 μ U/ml. Concentration above 20 μ U/ml confirms the presence of IR

ACUTE INSULIN RESISTANCE

Insulin resistance that occurs in chronic diseases, such as Type 2 diabetes, obesity and hypertension, normally takes months, years or even decades to develop. Hyperglycemia and insulin resistance in critically ill patients is characterized by rapid onset, developing in minutes, hours or days, and is thus termed acute insulin resistance.^[8] Major Surgical stress/trauma, sepsis and inflammation as well as acute stroke may result in acute insulin resistance. Therefore, it is not surprising to observe hyperglycemia in patients with those conditions without history of pre-existing diabetes.

Insulin resistance as a marker of surgical stress

Elective surgery causes a marked transient reduction in insulin sensitivity. The degree of the reduction is related to the magnitude of the operation and type of anaesthesia/ analgesia. It is not clear which mediators are the most important for the development of IR after

surgery. Nevertheless, marked insulin resistance can develop after elective surgery without concomitant elevations in cortisol, catecholamines or glucagon. The main sites for insulin resistance seem to be extrahepatic tissues, probably skeletal muscle, where preliminary data suggest that glucose transporting system is involved.^[9]

A novel approach to minimise insulin resistance after surgery suggests that simply pretreating patient with sufficient amounts of carbohydrates orally or parenterally instead of fasting can significantly reduce postoperative insulin resistance. In addition, postoperatively, provision of 400-600 kcal per day for first few days (1000-1500 ml glucose and amino acids containing maintenance solutions, such as Aminofluid®) seems to be a logical approach.

References:

1. McGarry J (2002). "Banting lecture 2001: dysregulation of fatty acid metabolism in the etiology of type 2 diabetes". *Diabetes* 51 (1): 7–18.
2. J R Flores-Riveros (1993). Insulin down-regulates expression of the insulin-responsive glucose transporter (GLUT4) gene: effects on transcription and mRNA turnover. 90. pp. 512-516.\
3. Paul S. MacLean_2002 (2002). "Exercise-Induced Transcription of the Muscle Glucose Transporter (GLUT 4) Gene". *Biochemical and Biophysical Research Communications* 292 (2): 409-414
4. Mlinar B, Marc J, Janež A, Pfeifer M. Molecular mechanisms of insulin resistance and associated diseases. *Clinica Chimica Acta* 375 (2007) 20–35
5. Abdelaziz Elamin A, Tuvemo T. Magnesium and insulin-dependent diabetes mellitus. *Diabetes Research and Clinical Practice*, 10 (1990) 203
6. Sales CH, Pedrosa LDFC . Magnesium and diabetes mellitus: Their relation. *Clinical Nutrition* (2006) 25, 554–562
7. McAuley KA, Williams SM, Mann JI, Walker RJ, Lewis-Barned NJ, Temple LA, Duncan AW (2001) Diagnosing

insulin resistance in the general population. Diabetes Care 24:460-464

8. Li Li & Messina JL. Acute insulin resistance following injury. Trends in Endocrinology and Metabolism Vol.20 No.9. 2009
9. Sunatrio S. Insulin Resistance in Surgical Critical Care Patients. In Bissett IP (editor). 2nd Clinical Nutrition Expert Meeting. Farmedia 2000.

POSTOPERATIVE INSULIN RESISTANCE

Iyan Darmawan

Introduction

Insulin resistance (IR) means that normal amounts of insulin are inadequate to produce a normal insulin response from fat, muscle and liver cells. Insulin resistance in fat cells reduces the effects of insulin and results in elevated hydrolysis of stored triglycerides. Increased mobilization of stored lipids in these cells elevates free fatty acids in the blood plasma. Insulin resistance in muscle cells reduces glucose uptake (and so local storage of glucose as glycogen), whereas insulin resistance in liver cells results in impaired glycogen synthesis and a failure to suppress glucose production.

1. How insulin resistance develops

Surgery and trauma triggers the release of stress hormones and cytokines^(1,2). Catecholamines, cortisol, glucagon and growth hormone independently cause IR, and potentiate each other. Cytokines such as Interleukin 6 and TNF- α also cause insulin resistance. IR affects all parts of metabolism and also other endocrine systems. Hyperglycemia and elevations of FFA levels are typical signs of insulin resistance. Protein breakdown increases and negative nitrogen balance is also associated with insulin resistance.

2. Metabolic and clinical outcomes from treating insulin resistance

When the effectiveness of insulin is reinstated by the use of iv insulin, these metabolic disturbances are reversed. More importantly, in critically ill surgical patients, this treatment was shown to reduce mortality by over 40%, due to reductions in sepsis, need of assisted ventilation, renal failure and polyneuropathy⁽³⁾ (Fig. 1).

Fig 1 .Clinical Results of Patients with Prolonged Severe Status(Stayed in ICU $\geq$ 1 week)

Van den Berghe G.et al Clin Invest 2005 115 (8) 2277-2286

	Conventional Insulin Therapy (224 cases)	Intensive Insulin Therapy (181 cases)	p
Mortality in ICU (number (%))	47(21)	21(12)	0.01
Cause of death (number)			0.7
sudden hemodynamic collapse	6	3	
MOF with confirmed infection	23	7	
source	16	10	
MOF accompanying SIRS	2	1	
Severe cerebropathy	59(26)	31(17)	0.01
Bacillema (number (%))			
Acute renal failure requiring CVVH (number (%))	58(26)	30(17)	0.02
Period of artificial respiration	18(8-24)	11(7-18)	0.03
Period of ICU stay	15(11-28)	14(9-24)	0.02

Other studies have suggested that the degree of insulin resistance is an independent factor explaining the variation in length of stay after uncomplicated surgery ⁽⁴⁾ (Fig. 2).

Insulin resistance & length of stay

Retrospective analysis of LOS for 53 patients with uneventful postop course.

The relative change in insulin sensitivity relates to LOS. The absolute change had no relation to LOS

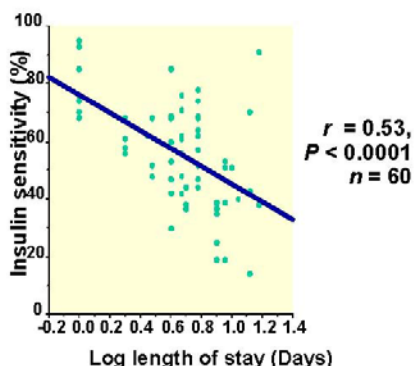


Fig 2. Thorell et al: Curr Opin Clin Nutr Metab Care 1999

3. Changes in glucose metabolism

Within minutes of the trauma, changes in all parts of metabolism begin to occur. The overall reaction is a change to catabolism.

Hyperglycaemia develops due to a simultaneous increase in glucose production, while glucose uptake in insulin sensitive cells (mainly muscle and fat tissue) becomes resistant to the action of insulin.

In muscle, the main target tissue for insulin, this hormone has reduced capacity to stimulate specific glucose transporting proteins facilitating glucose uptake, and glycogen formation is also blocked.

It is interesting to note that the changes occurring in glucose metabolism after surgery in otherwise healthy patients are very similar to those developing over years in patients with diabetes mellitus type 2. The degree of IR is related to the magnitude of the operation ⁽⁴⁾

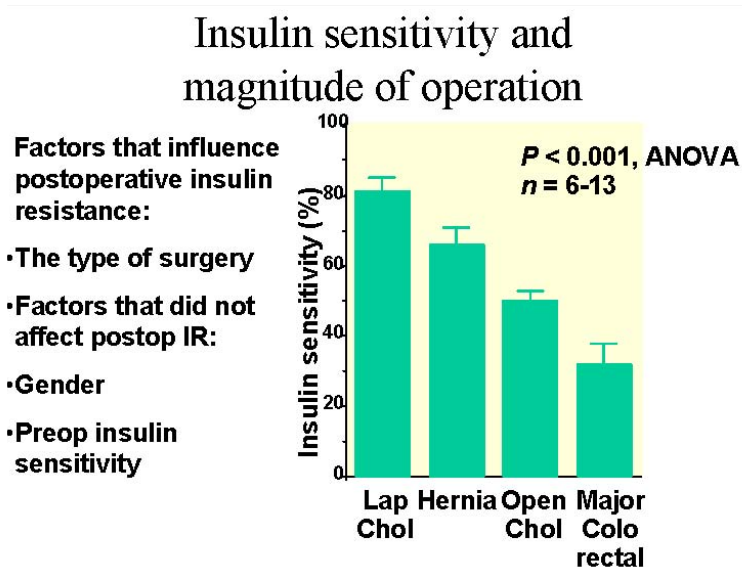
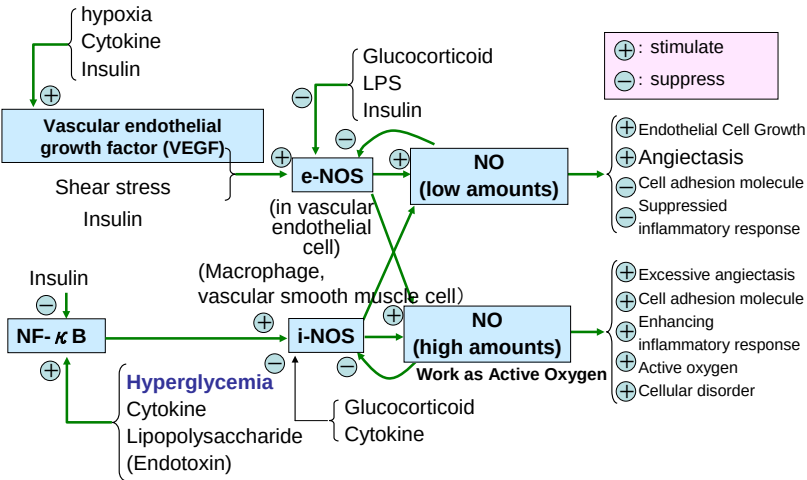


Fig 3. Thorell et al: Curr Opin Clin Nutr Metab Care 1999

Severe untreated hyperglycemia could result in Multiple Organ failure by the following complex mechanism ⁽⁵⁾

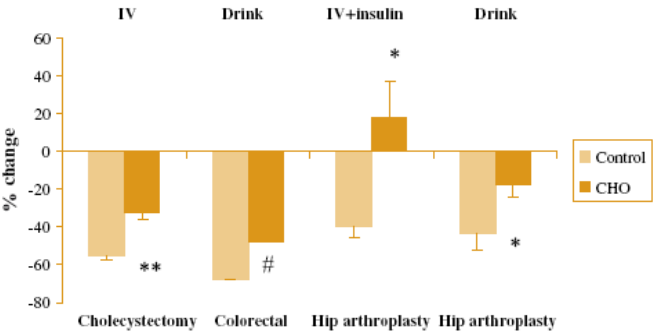
Fig 4 Mechanism by which Hyperglycemia Induces Multiple Organ Failure (hypothesis)



4. Proactive approach to insulin resistance

Preoperative carbohydrate loading

Preoperative carbohydrates reduce glucose production and enhances glucose uptake ⁽⁶⁾. When this treatment is combined with epidural analgesia for several days after major colorectal surgery, insulin resistance can be minimized to levels seen after laparoscopic cholecystectomies.



Intraoperative epidural blockade followed by postoperative epidural analgesia

Donatteli et al ⁽⁷⁾ studied sixty patients undergoing either hip or knee arthroplasty and concluded that epidural anesthesia and analgesia compared to general anesthesia followed by patient-controlled analgesia decreased the incidence of IR soon after surgery and 48 h after surgery in patients who were insulin-resistant before surgery.

6. Modern Fasting Guidelines

Over the last 2 decades the traditional routine of overnight fasting before elective surgery has been questioned, challenged and proven not to provide any additional safety over allowing patients to drink freely of clear fluids up until 2 hours before elective anaesthesia and surgery ⁽⁸⁾

In fact, many of the most common preoperative discomforts primarily thirst and to some extent headaches and hunger, can be avoided when the patient is allowed to drink in the morning before surgery.

Many European and North American Anaesthesia Societies have therefore updated their fasting guidelines and generally recommend that patients drink clear fluids up until 2 hours before anaesthesia. Solids, however, empty from the stomach much slower, and should not be taken later than 6 hours before anaesthesia. Patients with known slow gastric emptying for any reason should best be treated with more restriction, and generally be kept fasted for longer periods of time to reduce the risk of aspiration

References:

1. Giannoudis PV, Dinopoulos H, Chalidis B, Hall GM Surgical stress response Injury, Volume 37, Supplement 5, December 2006, Pages S3-S9

2. Sido B, Teklote J, Hartel M, Friess H, Büchler MW. Inflammatory response after abdominal surgery Review Article Best Practice & Research Clinical Anaesthesiology, Volume 18, Issue 3, September 2004, Pages 439-454
3. van den Berghe, G., et al., Intensive insulin therapy in the critically ill patients. N Engl J Med, 2001. **345**(19): p. 1359-67.
4. Thorell, A., et al Insulin resistance: a marker of surgical stress. Curr Opin Clin Nutr Metab Care, 1999. **2**(1): p. 69-78.
5. Langouche.L., et al: Intensive insulin therapy protects the endothelium of critically ill patients J.Clin.Invest, 2005 ; **115** : 2277-2286
6. Nygren J. The metabolic effects of fasting and surgery. Best Practice & Research Clinical Anaesthesiology Vol. 20, No. 3, pp. 429e438, 2006
7. Donatelli F, et al. Epidural Anesthesia and Analgesia Decrease the Postoperative Incidence of Insulin Resistance in Preoperative Insulin-Resistant Subjects Only. Anesth Analg 2007;104:1587-93.
8. Winslow E. Preoperative afsting . AJN, American Journal of Nursing: December 2010 - Volume 110 - Issue 12 - pp 12-13

REFEEDING SYNDROME

Iyan Darmawan

Refeeding syndrome was first described in Far East prisoners of war after the second world war. Starting to eat again after a period of prolonged starvation seemed to precipitate cardiac failure. The pathophysiology of refeeding syndrome has now been established. In starvation the secretion of insulin is decreased in response to a reduced intake of carbohydrates. Instead fat and protein stores are catabolised to produce energy.

This results in an intracellular loss of electrolytes, in particular phosphate. Malnourished patients' intracellular phosphate stores can be depleted despite normal serum phosphate concentrations. When they start to feed a sudden shift from fat to carbohydrate metabolism occurs and secretion of insulin increases. This stimulates cellular uptake of phosphate, which can lead to profound hypophosphataemia. This phenomenon usually occurs within four days of starting to feed again. Phosphate is necessary for the generation of adenosine triphosphate from adenosine diphosphate and adenosine monophosphate and other crucial phosphorylation reactions. Serum phosphate concentrations of less than 0.50 mmol/l (normal range 0.85-1.40 mmol/l) can produce the clinical features of refeeding syndrome, which include rhabdomyolysis, leucocyte dysfunction, respiratory failure, cardiac failure, hypotension, arrhythmias, seizures, coma, and sudden death. Importantly, the early clinical features of refeeding syndrome are non-specific and may go unrecognised.

Refeeding syndrome can occur with parenteral as well as enteral feeding.⁽¹⁾

Refeeding syndrome is a common, yet under-appreciated, constellation of electrolyte derangements that typically occurs in acutely ill, malnourished hospitalised patients who are administered glucose

solutions or other forms of intravenous or enteral nutrition. The hallmark of RFS is hypophosphataemia, but hypokalaemia and hypomagnesaemia are also common. Patients with various types of malignancies are at-risk for RFS, but very little exists in the oncologic literature about this disorder. As RFS can have many adverse metabolic, cardiovascular, haematologic and neurologic complications, practicing oncologist needs to be aware of the pathophysiology, risk factors and clinical manifestations to promptly recognise this important, and potentially fatal, metabolic disorder. ⁽²⁾

Independent risk factors for developing refeeding hypophosphataemia were: significant malnutrition measured as a Nutrition Risk Screening (NRS) score of three or more; less than 12 mmols total phosphate in the first day's PN regimen; and an initial rate of infusion of PN of more than 70% of calculated requirements. ⁽³⁾

The relationship between refeeding syndrome and delirium may be of particular significance in the elderly, since malnutrition, medical hospitalization, and delirium are prevalent phenomena in this population. ⁽⁴⁾

Lack of calorie intake with free access to water resulted in loss of body weight. Haemoconcentration was observed and feeding should be started with a low sodium, hypocaloric liquid formulation. During early refeeding, marked hypophosphataemia, haemodilution and slight edema developed. Vitamins B₁, B₁₂ and B₆ were depleted while serum free fatty acids, ketone bodies and zinc levels were abnormally high; abnormal liver function developed over the first week. The hormonal profile showed low IGF-I and insulin levels, and elevated IGF-binding protein-1 concentrations. Appetite-regulating hormones were either very low (leptin and ghrelin) or showed no marked difference from the control group (peptide YY, agouti-related peptide, alpha-melanocyte-stimulating hormone, neuropeptide Y and pro-opiomelanocortin). Appetite was low at the

beginning of refeeding and a transient increase in orexin and resistin was observed coincidentally with an increase in subjective hunger.⁽⁵⁾

With regard to parenteral administration of nonprotein calorie and amino acids to severe malnourished patients, it should be initiated with care and start very low and uptitrated slowly. Maintenance solutions containing 30 g amino acids, 7.5% glucose supplemented with maintenance dose of electrolytes and microminerals are highly recommended before switching to full dose parenteral alimentation. Typical new generation maintenance solutions are Aminofluid & B Fluid.

Reference:

1. Stephen D Hearing Editorial Refeeding syndrome. BMJ 2004;328:908-909
2. Marinella MA Refeeding syndrome in cancer patients .Int J Clin Pract. 2008 Mar;62(3):460-5..
3. Vanessa A. Marvin¹ Contact Information, David Brown², Jane Portlock² and Callum Livingstone. Factors contributing to the development of hypophosphataemia when refeeding using parenteral nutrition Pharmacy World & Science, Volume 30, Number 4 / August, 2008
4. Caplan JP..Too much too soon? Refeeding syndrome as an iatrogenic cause of delirium.Psychosomatics. 2008 May-Jun;49(3):249-51.
5. Korbonits M, Blaine D, Elia M, Powell-Tuck Metabolic and hormonal changes during the refeeding period of prolonged fasting. J.Eur J Endocrinol. 2007 Aug;157(2):157-66.

UPDATE ON NUTRITION SUPPORT IN TRAUMA

Iyan Darmawan

Introduction

Metabolic and nutritional profile of patients with major trauma are characterized by hypercatabolism.^(1,2) In the absence of exogenous provision of substrates, amino acids are “autocannibalized” from endogenous sources. Initially, skeletal muscle proteolysis is followed by erosion of visceral structural elements and circulating proteins. The resultant acute protein malnutrition is associated with cardiac, pulmonary, hepatic, gastrointestinal, and immunologic dysfunctions. Late infectious complications can prolong the hypermetabolic or hypercatabolic state, eventually resulting in multiple-organ failure. 1) *Does early and aggressive nutrition support improve patient outcome?* 2) *What is the preferred route of substrate delivery?* 3) *Do “immune-enhancing” diets offer additional benefits?*

Pathophysiology of Trauma

The pathophysiology of trauma includes an immediate cardiovascular response, an inflammatory response occurring several hours after the injury, and finally a metabolic response⁽³⁾

Cardiovascular response

The cardiovascular response associates hemorrhage, tissue damage, pain and anxiety and has three phases:

- First, heart rate and total peripheral vascular resistance increase to maintain blood pressure.
- After a loss of a third of blood volume, blood pressure falls and is accompanied by bradycardia and syncope.
- Finally, when about 44% of blood is lost, heart rate increases again massively.

Inflammatory response

During the inflammatory response there is an increased production of cytokines (TNF- α , IL-1, IL-6, IL-10). These cytokines are probably produced in the gut (via stimulation of the gut associated lymphoid tissue) as well as locally at the wounded tissue

Metabolic response

Finally, the metabolic response consists mainly of hypermetabolism, mediated by the stimulation of catabolic hormones (glucagons, catecholamines and corticoids) and insulin resistance. Associated with inadequate nutrition, the administration of drugs as glucocorticoids and physical immobilization, this neuroendocrine response leads to protein breakdown to amino acids which are used to produce de novo glucose in the liver.

What is the extent of protein loss during trauma?

Hill, using body composition analysis, reported that daily muscle protein loss in surgical and trauma patients average 250 g ⁽²⁾. In addition to gluconeogenesis, amino acids arriving at the liver are redirected to the synthesis of acute phase proteins ⁽⁴⁾

What is the optimum Calorie and protein requirement?

Like other critically-ill and surgical conditions, current recommendation of nonprotein calorie (NPC) intake in patients with trauma is 25 kcal/kg/day⁽³⁾. However, with increasing evidence that muscle wasting and outcome from critical illness are not favourably influenced by increasing energy intakes, and achieving positive energy balance, hypocaloric feeding has been proposed as a means of providing energy at a minimum level so as not to negatively impact on metabolic adaptive responses to injury and stress

Three separate studies emphasize the benefits of hypocaloric feeding, particularly during acute phase of trauma, and after resuscitation has succeeded.

In overweight or obese patients, Ibrahim et al randomized 150 patients in the ICU who had an average BMI of 29.3 kg/m² to receive 25 kcal/kg per day fed enterally either at time of admission or after 4 days. The latter group in aggregate received 20% of energy given to the first group. They found that a reduced energy intake was associated with less pneumonia (37 vs 23; *p* .02), *antibiotic days* (12.4 vs 7.5; *p* .001), and *ventilation days*.⁽⁵⁾

In contrast to energy intake in critical illness, protein requirements are markedly increased. In a randomized controlled trial of patients with major burns, a high-protein intake significantly reduced mortality.⁽⁶⁾ 10–20 kcal/kg of ideal or adjusted weight and 1.5–2 g/kg ideal weight of protein may be beneficial during the acute stress response.⁽⁶⁾

25% to 66% of goal calories may be sufficient. Early PN improves outcome.⁽⁷⁾

Which is the preferred route of delivery?

The EAST Practice Management Guidelines Workgroup published the following recommendations⁽⁸⁾ :

RECOMMENDATIONS

A. Level I

Patients with *blunt and penetrating abdominal injuries* should, when feasible, be fed enterally because of the lower incidence of septic complications compared with parenterally fed patients.

B. Level II

Patients with *severe head injuries* should preferentially receive early enteral feeding, since outcomes are similar compared with parenterally-fed patients. If early enteral feeding is not feasible or not tolerated, parenteral feedings should be instituted.

C. Level III

1. In severely injured patients, TPN should be started by day 7 if enteral feeding is not successful.
2. Patients who fail to tolerate at least 50% of their goal rate of enteral feedings by post-injury day 7 should have TPN instituted but should be weaned when > 50% of enteral feedings are tolerated.

What if enteral nutrition is inadequate?

Recently a metaanalysis was conducted by Sena et al ⁽⁹⁾ which concluded as follows:

1. Early PN supplementation to 249 trauma patients who were EN tolerant increased nosocomial infections (RR 1.6), Blood stream infections SI (RR 2.8), and mortality (RR 2.3)
2. EN tolerant was defined as the ability to take $\geq$ 1000 kcal
3. Early PN was defined as giving at least 750 kcal/day within one week post trauma
4. Early EN and PN remained associated with increased risk of nosocomial infection, even with lower tolerant threshold of enteral intake (500 kcal) in the first week (RR 2.5; 95% CI, 1.4 to 4.5).
5. Blood glucose concentrations are comparable in the early PN supplementation and control group. Therefore, reasons for increased infection and mortality are not hyperglycemia

6. Increased albumin concentration observed in patients with EN + early PN was not associated with improved outcome
7. Fat emulsion was suspected to be the “culprit” because it can suppress neutrophil and lymphocyte functions

Therefore, if enteral nutrition can be given at 500 to 1000 kcal/day, supplementation with PN should be started only after 7 days of trauma.

Is there any added value of immune-enhancing formula in patients with trauma? Is arginine beneficial or harmful?

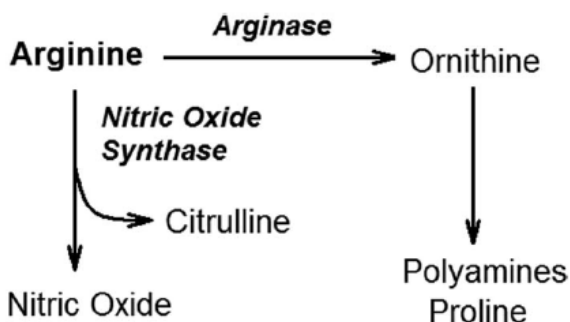
Among the amino acids, arginine has been reported to enhance wound healing and immune function. Its mechanism of action may be partly mediated by an increase of growth hormone secretion. ^(3,4)

In general, immune enhancing formula, aka immunonutrition contains at least glutamine, arginine, and omega-3. Glutamine is the essential fuel for lymphocyte and enterocytes. Use of immune-enhancing formula in septic patients are currently not recommended, in view of the theoretical pathway of arginine. Heyland *et al.* hypothesized that there could be adverse affects caused by immunonutrition in critically ill patients with ongoing infection and sepsis. ⁽¹⁰⁾ Arginine is postulated to be the causative agent, primarily because of possible conversion to nitric oxide with potentially detrimental vasodilatory effects.

However, the situation in trauma is totally different. Tsuei BJ et al ⁽¹¹⁾ found that supplemental enteral arginine is absorbed in injured patients and increases arginine levels. Supplemental arginine appears to be metabolized to ornithine. Increased arginase enzyme activity in peripheral blood mononuclear cells may be a contributor.. While, in theory, supplemental arginine

might be shunted to the production of nitric oxide with resultant hypotension, Tsuei et al did not see evidence of this in their patient population.

In fact, there may be crucial differences in the metabolism of arginine and production of nitric oxide in trauma and septic patients. Ochoa *et al.* demonstrated a significant decrease in plasma nitric oxide metabolites in trauma patients when compared to septic patients (12 $\mu\text{mol/liter}$ versus 63 $\mu\text{mol/liter}$)



Which immune-enhancing formula and what is the dosage?

In Indonesia, immune-enhancing formula is available as Neomune[®], containing NPC 200 kcal; Protein 12,5 g plus glutamine (1.25 g), arginine (2.5 g), fish oil (omega-3) (1.11 g) per sachet

Dosages as little as 3 –5 sachets should be administered during the first week of trauma.

References:

1. Biffl WL et al. Nutrition support of Trauma Patient Nutrition 18:960 –965, 2002 ©Elsevier Science Inc., 2002
2. Hill GL. Disorders of Nutrition and Metabolism in Clinical Surgery: Understanding and Management. Churchill Livingstone 1992

3. Genton L, et al., Basics in Clinical Nutrition: Nutritional support in trauma, e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism (2009)
4. Reid CL , I.T. Campbell LT. Nutritional and metabolic support in trauma, sepsis and critical illness. *Current Anaesthesia & Critical Care* (2004) 15, 336–349
5. Jeejeebhoy. Permissive Underfeeding of the Critically Ill Patient. *Nutrition in Clinical Practice* 19:477–480, October 2004
6. Boitano M. Hypocaloric Feeding of the Critically Ill *Nutrition in Clinical Practice*, Dec 2006; vol. 21: pp. 617 – 622.
7. Stapleton RD, Jones N, Heyland DK. Feeding critically ill patients: what is the optimal amount of energy? *Crit Care Med*. 2007 Sep;35(9 Suppl):S535-40.
8. Jacobs DG et al. Practice Management Guidelines For Nutritional Support Of The Trauma Patient *J Trauma*. 57(3):660-679, September 2004
9. Sena et al. Early Supplemental Parenteral Nutrition Is Associated with Increased Infectious Complications in Critically Ill Trauma Patients *J Am Coll Surg* 2008;207:459-467© 2008
10. Heyland, D. K., and Samis, A. Does immunonutrition in patients with sepsis do more harm than good? *Int. Care Med*. **29**: 669, 2003.
11. Tsuei BJ et al. Supplemental Enteral Arginine Is Metabolized to Ornithine In Injured Patients. *Journal of Surgical Research* 123,17-24 (2005)

FLUID AND NUTRITION MANAGEMENT IN ACUTE PANCREATITIS

Iyan Darmawan

Introduction

Adequate fluid and nutrition therapy is still a major medical problem in patients with acute pancreatitis.

Acute pancreatitis occurs when there is activation of pancreatic enzymes within the pancreas with subsequent autodigestion. An initiating event causes the extrusion of zymogen granules from acinar cells, into the interstitium and activates trypsinogen into trypsin. This activation leads to various pathophysiological changes from mild inflammation to necrosis (frequently hemorrhagic) and development of peripancreatic infiltration. The pathological findings, which correlate with clinical severity, range from mild oedema to pancreatic necrosis. Secondary infection and splanchnic hypoperfusion can lead to the development of septic complications and subsequent multiorgan failure.

The two most common causes of acute pancreatitis are alcohol over consumption and gallstones, although etiology includes other factors (hypertriglyceridemia, drugs, iatrogenic ERCP, trauma, idiopathic, etc). Together, they represent more than 80% of cases ^(1,2)

Clinical Presentation

Mid epigastric pain which radiates to the back associated with nausea and vomiting. Patients often appear very ill. Findings that suggest severe pancreatitis include hypotension and tachypnea with decreased basilar breath sounds. Flank ecchymoses (Grey Turner's sign) or periumbilical ecchymoses (Cullen's sign) indicate hemorrhagic pancreatitis.⁽²⁾

Lab findings:

1. Leucocytosis, hemoconcentration and hyperglycemia are common.
2. Dehydration, pre-renal azotemia
3. Elevated amylase level often confirms the clinical diagnosis
4. Serum lipase is a more reliable diagnostic marker of AP than serum amylase. Urinary strip tests for trypsinogen activation peptide (TAP) and trypsinogen-2 provide a reliable early diagnosis of AP ⁽³⁾
5. Radiology : CT scan may reveal necrosis, pseudocyst and abscess

Treatment

1. NPO (nothing per oral)
2. IV fluid resuscitation (isotonic crystalloids such as Asering, Lactated Ringer) in severe cases with hypovolemia and hypotension. Severe acute pancreatitis is associated with microcirculatory impairment, increased gut permeability and metabolic changes
3. Nutrition
4. Pain control
5. Antibiotics, octreotide etc.

Nutritional Management ⁽⁴⁾

–Aggressive nutritional support is not required for mild to moderate forms of acute pancreatitis. In this regard, AminoFluid ® 1-2 L is suitable to provide water, electrolytes and microminerals as well as maintenance requirement of glucose and amino acids. . Nutritional therapy has to be considered earlier if restoration of oral feeding is delayed. In severe pancreatitis nutritional support is essential.

– The route of nutrient delivery (parenteral/enteral) should be determined by patient tolerance. Enteral

should be attempted in all patients. The clinician should monitor intakes carefully to ensure adequate nutritional support as well as avoiding nutrient excess. Many patients will require a combination of enteral and parenteral nutrition.

- Patients with severe disease, complications or the need for surgery require early nutritional support to prevent the adverse effects of nutrient deprivation (enteral and/or parenteral nutrition is possible according to the patient condition).
- Some authorities recommend early jejunal feeding with an elemental diet and others parenteral nutrition with concomitant enteral given to tolerance;
- When side effects occur or the caloric goal cannot be achieved, enteral nutrition should be combined with parenteral nutrition.
- The combined approach allows the achievement of nutritional goals most of the time.
- The use of intravenous lipids as part of parenteral nutrition is safe only when severe hypertriglyceridemia (<10 mmol/L) is avoided. However, the concentration of plasma triglycerides should be $<3-4$ mmol/L, due to metabolic problems connected with hypertriglyceridemia.
- When nutritional support is necessary, start with enteral feeding by jejunal feeding tube (when the caloric goal cannot be reached, give additional parenteral support).

Recommended dosage of nutrients (over feeding should be avoided)

Substrate	Quantity
Energy	~ 25 kcal/kg/day
Protein	1.2-1.5 g/kg/day

Carbohydrate	3-6 g/kg/day according to BG (aim < 7 mmol/L) or (<126 mg/dl)
Lipids	Up to 2 g/kg/day correspond to blood triglyceride level (aim < 3-4 mmol/L)

– When enteral nutrition is not possible (e.g. prolonged paralytic ileus), combine parenteral nutrition with a small content of immuno-enhancing diet eg Neomune® (10–30 ml/hr). ⁽⁴⁾

Conclusion

Treatment of severe acute pancreatitis including initial fluid resuscitation, a moderate and hypocaloric parental nutrition as the preferred route for nutritional support and a non-strict glucose control should be encouraged. ⁽⁵⁾

In SAP, oral intake is inhibited by cytokine induced anorexia, ileus, duodenal compression and consequent nausea and vomiting. Traditionally patients were kept 'nil by mouth' to minimise pancreatic stimulation as this was thought to exacerbate inflammation of the pancreas. The importance of nutrition became clear when reduced mortality and complications were reported in patients supported with parenteral nutrition (PN) as compared with no nutritional support. Thereafter parenteral nutrition became standard care in SAP.

However disuse of the gut leads to a degree of intestinal ischemia and consequent decrease in gut mucosal barrier function. Bacterial translocation results with infected pancreatic necrosis and sepsis. Absorption of bacterial products such as endotoxins further stimulates a generalised inflammatory response. It has been suggested that enteral nutrition (EN) may help preserve mucosal function and limit the stimulus to the

inflammatory response pathways; thus attenuating disease severity, improving therapeutic results. However, intra-gastric nutrition increases pancreatic exocrine secretions, which may aggravate pancreatitis. This led to investigation of post-pyloric naso–jejunal enteral nutrition. ⁽⁶⁾

Note: Neomune® Each 48 g/ sachet, contains :Energy 200 kcal Protein 12.5 g (Casein 8.76 g Arginine 2.50 g Glutamine 1.25 g)Carbohydrate 25.01 g,Fat 5.79 g,Vitamins, Minerals

References:

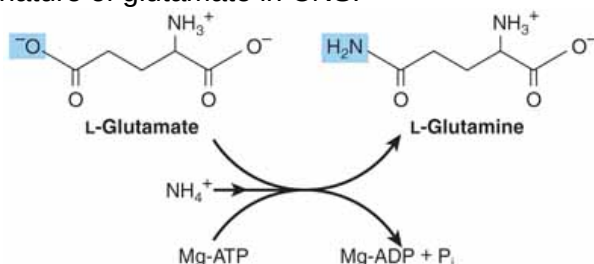
1. B. W. M. Spanier et al Epidemiology, aetiology and outcome of acute and chronic pancreatitis: An update. Best Practice & Research Clinical Gastroenterology Vol. 22, No. 1, pp. 45–63, 2008
2. Brenner M, Safani M. Critical Care Medicine. Current Clinical Strategy Publishing 2002-2003. Pp 101-104
3. Ahmed Z. Al-Bahrani, Basil J. Ammori Clinical laboratory assessment of acute pancreatitis Clinica Chimica Acta 362 (2005) 26–48
4. Meier RF ,Sobotka L. Basics in Clinical Nutrition: Nutritional support in acute and chronic pancreatitis e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism, Volume 5, Issue 1, February 2010, Pages e58-e62
5. Gunilla Eckerwall, Hanna Olin, Bodil Andersson, Roland Andersson Fluid resuscitation and nutritional support during severe acute pancreatitis in the past: What have we learned and how can we do better? Clinical Nutrition (2006) 25, 497–504
6. Ahmad Al Samaraee et al. Nutritional strategies in severe acute pancreatitis: A systematic review of the evidence. the surgeon 8 (2010) 105 – 110

IS GLUTAMINE USEFUL OR HARMFUL IN HEAD INJURY PATIENTS?

Iyan Darmawan

Introduction

Glutamine is a conditionally-essential and the most abundant free amino acid in the plasma and skeletal muscle. Nowadays, it is regarded as most important component immunonutrient, besides arginine and n3-fatty acid. Its role in critically-ill patients has long been established. However, there is concern about its safety in patients with head injury in view of the excitatory nature of glutamate in CNS.



Endogenous glutamine is produced from amidation of glutamate catalyzed by glutamine synthetase (Source: Murray RK, Bender DA, Botham KM, Kennelly PJ, Rodwell VW, Weil PA: Harper's Illustrated Biochemistry, 28th edition. McGraw-Hill Companies)

Beneficial effects of Glutamine

Mobilization of glutamine provides substrate for gut, immune cells, and kidneys. Beneficial effects of glutamine include the following: anti-oxidant effects (as a precursor of glutathione or γ -glutamyl-cysteinyl-glycine), inducing production of heat shock proteins, maintaining gut barrier function by providing fuel for enterocytes, as an energy substrate for lymphocytes and neutrophils, and stimulation of nucleotide synthesis .

In elective surgical patients, glutamine reduced infectious complications and length of hospital stay, without adverse effects on mortality. Positive results

were also seen in critically ill patients, in whom supplemental glutamine reduced complications and mortality rate ⁽¹⁾.

Glutamine supplementation led to asinificant reduction of hyperglycemia and a significant reduction in the number of patients requiring insulin ⁽²⁾.

When exogenous glutamine is administered enterally, there is an immediate uptake in the upper part of the gastrointestinal tract. The effects of enteral glutamine supplementation on plasma concentration are highly variable and often marginal in size. The major portion of the administered glutamine is utilized in the gut itself by enterocytes and immune competent cells and the rest is utilized in the liver, and through this first pass elimination, the major part of the given dose is utilized. Still, as enterocytes and immune competent cells are the target cells, this may be sufficient for an improvement in the clinical outcome, but the uneven distribution may also be a problem. In critical illness, an additional problem may be the uncertainty concerning the absorption and utilization of any enterally administered nutrient ⁽³⁾.

There have been recommendations to support the addition of enteral glutamine to standard non-glutamine supplemented enteral formulas for trauma and mixed intensive care unit patients. Standard dosing of glutamine powder mixed with water should provide 0.3-0.5g/kg/d and be given in two or three divided doses via the feeding tube ^(4,6).

Role of Glutamine in Patients with Head Injury ⁽⁴⁾

Nutritional support is imperative to the recovery of head-injury patients. Hypermetabolism and hypercatabolism place this patient population at increased risk for weight loss, muscle wasting, and malnutrition. Nutrition management may be further complicated by alterations in gastrointestinal motility. Resting energy expenditure should be measured using indirect calorimetry and protein status measured using urine urea nitrogen.

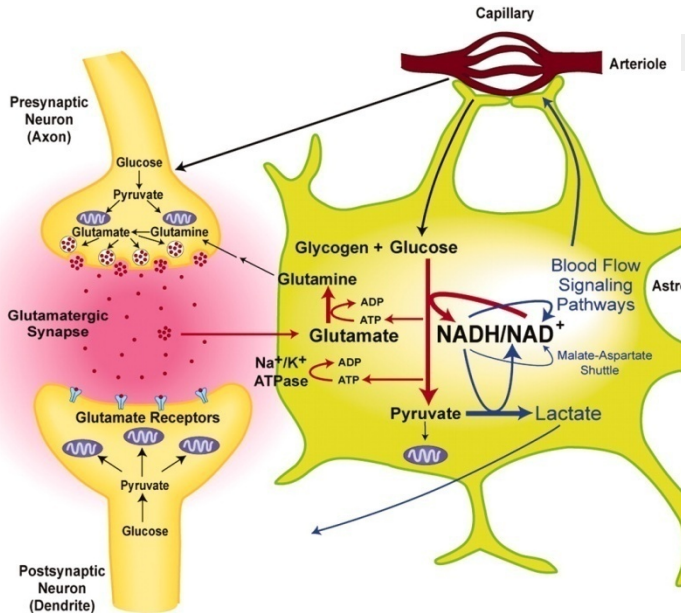
Providing early enteral nutrition within 72 hours of injury may decrease infection rates and overall complications. 2.2 or 1.5g protein/kg/d to patients after severe head injury. The provision of full-strength, full-rate enteral feeding of 2.2g protein/kg/d for 10 d resulted in a cumulative positive nitrogen balance of + 9.2g, whereas patients receiving 1.5g protein/kg/d produced a cumulative negative nitrogen balance of - 31.2g. A 24-h UUN determination $[\text{nitrogen balance} = (\text{protein intake}) / (6.25) - (\text{UUN excretion} + 3 - 5\text{g})]$.

For neurosurgical patients, in particular patients with head injuries, there are concerns that the elevated level of glutamate interstitially in the brain may be influenced by exogenous glutamine supplementation. The elevated glutamate has been reported to be an indicator of an unfavorable outcome. However, these observations are perhaps more anecdotal than evidence based.

In adult human studies, transient elevations of glutamate were linked to periods of seizure activity, very high extracellular glutamate was associated with focal contusions and secondary ischaemic events, and there was strong correlation between sustained high ICP, poor outcome and high extracellular glutamate. Therefore, there are concerns that glutamine may result in an elevation of glutamate.

However, in a safety study, elevated plasma glutamine concentration secondary to exogenous glutamine supplementation did not affect plasma glutamate or intracerebral glutamate levels, as monitored by microdialysis. Furthermore, the efflux of glutamine from the brain was also unaffected by exogenous glutamine supplementation. Theoretically, there could be an impairment of the glutamate elimination via the glutamine pathway if the efflux of glutamine from the brain was diminished. In conclusion, there is no contraindication of using glutamine to head trauma

Endogenous Glutamate-Glutamine cycle



Regulation of blood flow in activated human brain by cytosolic NADH/NAD⁺ ratio

Initially, glial cells release glutamine, which is then taken up into presynaptic terminals and metabolized into glutamate by glutaminase (a mitochondrial enzyme). Glutamate can also be produced by transamination of 2-oxoglutarate, an intermediate in the Citric acid cycle.

The glutamate that is synthesized in the presynaptic terminal is packaged into synaptic vesicles by the transporter VGLUT. Once the vesicle is released, glutamate is removed from the synaptic cleft by excitatory amino acid transporters (EAATs), of which there are five types. Glutamate taken up by glial cells is then converted into glutamine by glutamine synthetase, and transported out of the cells into the nerve terminal. This allows synaptic terminals and glial cells to work together in order to maintain a proper supply of glutamate (Picture from (5))

patients and studies investigating if glutamine supplementation to this patient group may have advantageous effects upon outcome are encouraged. ⁽³⁾

Early enteral nutrition containing glutamine and probiotics in brain trauma patients decreases infectious morbidity and shortens the period of time in the ICU ⁽⁶⁾.

Recently, it has been found that glutamine levels are almost doubled in the ventricular fluid of patients with head injury, as compared with its levels in the lumbar spinal fluid of normals undergoing myelography. These results demonstrate the ability of glutamine to protect brain tissue (hippocampus) in vitro against hypoxic damage. Glutamic acid, a precursor of glutamine, elicited an opposite effect ⁽⁷⁾.

Safety of Glutamine in Humans ⁽⁸⁾

A series of dose-response studies was conducted to evaluate the clinical safety, pharmacokinetics, and metabolic effects of L-glutamine administered to humans.

[Study 1] Initial studies in normal individuals evaluated the short-term response to oral loads of glutamine at doses of 0, 0.1, and 0.3 g/kg. (That's a 7.5g or 22.5g ORAL dose for an average 75kg person). A dose-related increase in blood glutamine occurred after oral loading and elevation of amino acids known to be end products of glutamine metabolism occurred (including alanine, citrulline, and arginine). No evidence of clinical toxicity or generation of toxic metabolites (ammonia and glutamate) was observed.

[Study 2] Glutamine was infused intravenously in normal subjects over 4 hr at doses of 0.0125 and 0.025 g/kg/hr.

[Study 3] In addition, glutamine was evaluated as a component of parenteral nutrition solutions (0.285 and 0.570 g/kg/day) administered for 5 days to normal subjects. Intravenous administration of glutamine was well tolerated without untoward clinical or biochemical effects. (Again no increased Glutamate production) Subsequent studies in patients receiving glutamine-

enriched parenteral nutrition for several weeks confirmed the clinical safety of this approach in a catabolic patient population.

In addition, nitrogen retention appeared to be enhanced when glutamine was administered at a dose of 0.570 g/kg/day in a balanced nutritional solution providing adequate calories (145% of basal) and protein (1.5 g/kg/day).

CONCLUSION

Glutamine has been proven useful and can be given safely to critically ill patients, including those with head injury.

Footnote: In Indonesia, immune-enhancing formula is available as Neomune® , containing NPC 200 kcal; Casein 8.76 g, glutamine (1.25 g), arginine (2.5 g), fish oil (omega-3) (1.11 g) per sachet.

References:

1. Mizock BA. Immunonutrition and critical illness: An update Nutrition 26 (2010) 701–707 Elsevier
2. Wischmeyer PE. Glutamine: role in critical illness and ongoing clinical trials. Current Opinion in Gastroenterology 2008,24:190–197
3. Wernerman J. Clinical Use of Glutamine Supplementation J. Nutr. 138: 2040S–2044S, 2008
4. Vizzini A. Aranda-Michel J Nutritional support in head injury , Nutrition (2010), doi:10.1016/j.nut.2010.05.004
5. Andrei G. Vlassenko, Melissa M. Rundle, Marcus E. Raichle *, and Mark A. Mintun . Regulation of blood flow in activated human brain by cytosolic NADH/NAD⁺ ratio. PNAS February 7, 2006 vol. 103 no. 6
6. Falcão de Arruda I.S. and de Aguiar-Nascimento JE. Benefits of early enteral nutrition with glutamine and probiotics in brain injury patients. Clinical Science (2004) 106, 287–292

7. Schurr A, Changaris DG and Rigor BM Glutamine protects neuronal function against cerebral hypoxia: a study using the in vitro hippocampal slice preparation Brain Research, 412 (1987) 179-181 179 Elsevier
8. Ziegler TR; Benfell K; Smith RJ; Young LS; Brown E; Ferrari-Baliviera E; Lowe DK; Wilmore DW. Safety and metabolic effects of L-glutamine administration in humans JPEN J Parenter Enteral Nutr 1990 Jul-Aug;14(4 Suppl):137S-146S

GLUTAMINE MANAGES SIDE EFFECTS OF CANCER TREATMENT

Iyan Darmawan

Glutamine is the most plentiful protein building block (amino acid) in the body and is used for the processes that make energy. Most of the glutamine is found in skeletal muscle. Glutamine fuels immune cells, connective tissue and the lining of the gastrointestinal tract. In addition to its role as an immunonutrient, often combined with arginine and omega-3 fatty acid (eg. Neomune[®]), glutamine has been recently used for managing side effects of cancer treatment.

Why Glutamine is Important

Our bodies can make glutamine from BCAA (branched-chain amino acids) and glutamate.. During times of stress glutamine becomes essential and we may need extra amounts. An additional 30 to 40 grams of glutamine per day may be needed.

Glutamine depletion in host tissues occurs in tumor-bearing rats. Glutamine supplementation can attenuate loss of protein in the muscle in tumor-bearing animals and protect immune and gut-barrier function during radiochemotherapy in patients with advanced cancer. ⁽¹⁾

Glutamine appears to be the major energy source for intestinal epithelium. It has been shown to be effective in reducing the severity of radiation-induced mucosal injury of bowel in rats. Glutamine supplementation of an elemental diet resulted in less weight loss, increased mucosal weight of the jejunum and colon, longer survival, and a lower incidence of bacteremia among rats treated with methotrexate. Thus, Oral glutamine plays an important role in the preservation of intestinal mucosa integrity after radiotherapy and chemotherapy ⁽²⁾

In patients with cancer the use of glutamine may help with symptoms ⁽³⁾ of

- Diarrhea
- Inflammation of the mouth lining (mucositis)
- Sore mouth and throat (stomatitis)
- Tingling in fingers and toes (peripheral neuropathy)

Glutamine had been used with good results in those patients receiving:

- Radiation therapy
- Bone Marrow transplantation
- The chemotherapy agents paclitaxel or 5-fluorouracil (5-FU)

References:

1. Yoshida S, et. Glutamine Supplementation in Cancer Patients Nutrition Volume 17, Number 9, 2001
2. Huang EY, Leung SW, Wang CJ, et al.: Oral glutamine to alleviate radiation-induced oral mucositis: a pilot randomized trial. Int J Radiat Oncol Biol Phys 46 (3): 535-9, 2000.
3. Savarese DMF. Prevention of chemotherapy and radiation toxicity with glutamine CANCER TREATMENT REVIEWS 2003; 29: 501–513)

NUTRITION SUPPORT IN THE ELDERLY HOSPITALIZED PATIENTS

Iyan Darmawan

Introduction

Although UN agreed cutoff is 60+ years to refer to the older population, most developed world countries have accepted the chronological age of 65 years as a definition of 'elderly' or older person ^(1,2)

Out of 197 elderly patients studied using WHO criteria of BMI ⁽³⁾. According to the body mass index cutoff points recommended by the World Health Organization, 29.7% of subjects were classified as undernourished and 43.8% as eutrophic.

The elderly eat considerably smaller amounts of food and eat less often than the young. Especially at times of high energy requirements such as acute or chronic illness, this leads to an energy deficit and general malnutrition. ⁽⁴⁾ Moreover muscle mass deficit, i.e. sarcopenia, is a frequent comorbid situation.

Factors that can cause poor appetite or poor food intake in elderly hospitalized patients ⁽⁵⁾

- Mental illness (e.g. depression) Neurological disease (e.g. dementia, Parkinson's disease, stroke)
- Chronic debilitating disease (e.g. multiple sclerosis, motor neurone disease, osteoporosis, arthritis)
- Malignant disease and its treatment
- Poor dentition
- Gut dysfunction (e.g. acid reflux, nausea, vomiting, diarrhoea, constipation, diverticular disease)
- Effects of medication (e.g. sedation)

- Side-effects of medication (e.g. drowsiness, gut dysfunction).

Furthermore, In the gastrointestinal (GI) tract specifically, the overall aging effects alter the sensory response and GI motility, and decrease muscle strength and digestive enzyme secretions. Ultimately, decreased absorption of both macronutrients (energy) and micronutrients (vitamins and minerals) is seen. The eating process is negatively affected with sensory losses even before the internalization of foods. Sensory losses tend to progress more rapidly after 70 years of age, but can become noticeable around 60 years (Schiffman & Graham, 2000). Decreases in the acuity of eyesight, smell, and taste often lead to deficits in energy consumption with direct associations for impaired protein and micronutrient status. These possible deficiencies impact function and immunity. While chemosensory losses occur naturally with age, certain disease states (such as cancer), medications, surgical interventions, malnutrition and environmental exposure also complicate the situation. Along with taste impairments, dentition can greatly influence consumption. Loss of teeth and gum diseases are common in the elderly. These conditions make chewing more difficult and limit the food choices. ⁽⁶⁾

EN (Neomune®, PanEnteral® and Proten®) by means of ONS (oral nutrition supplement) is recommended for geriatric patients at nutritional risk, in case of multimorbidity and frailty, and following orthopaedic-surgical procedures. In elderly people at risk of undernutrition ONS improve nutritional status and reduce mortality. After orthopaedic-surgery ONS reduce unfavourable outcome. TF (tube feeding) is clearly indicated in patients with neurologic dysphagia. In contrast, TF is not indicated in final disease states, including final dementia, and in order to facilitate patient care ⁽⁷⁾

PN support should be instituted in the older person facing a period of starvation of more than 3 days when oral or enteral nutrition is impossible, and when oral or enteral nutrition has been or is likely to be insufficient for more than 7–10 days⁽⁸⁾ Partial daily supplementation with average 1 L of Aminofluid® is very helpful in elderly patients with moderate dehydration and anorexia. When deemed necessary in malnourished patients addition of 10% Amino acids (Amiparen®) and 20% fat emulsion is reasonable. Aminofluid® has beneficial effects of boosting appetite and reducing fatigue, thanks to its high BCAA content and complete microminerals.

References:

1. Keep fit for life. Meeting the nutritional needs of older persons. Geneva, World Health Organization, 2002.
2. (D. Volkert et al. ESPEN Guidelines on Enteral Nutrition. Clinical Nutrition (2006) 25, 330–360)
3. (A. K. Coelho et al. / Nutrition 22 (2006) 1005–1011)
4. A.A. Rizvi / International Journal of Diabetes Mellitus 1 (2009) 26–31
5. Smith A. Nutrition in elderly women. WOMEN'S HEALTH MEDICINE© 2004 The Medicine Publishing Company Ltd p 34
6. Brogan KE, K-L. Catherine Jen K-L, Nutrition in the Elderly Handbook of Assessment in Clinical Gerontology (Second edition), 2010, Pages 357-380
7. D. Volkert et al. ESPEN Guidelines on Enteral Nutrition. Clinical Nutrition (2006) 25, 330–360
8. Sobotka L. ESPEN Guidelines on Parenteral Nutrition: Geriatrics. Clinical Nutrition 28 (2009) 461–466

UPDATE ON CANCER CACHEXIA :

Q & A

Iyan Darmawan

Introduction

Cachexia is clinical syndrome characterized by severe weight loss, anorexia, early satiety, weakness and edema. Cachexia is almost invariably found in chronic diseases including cancer, chronic obstructive pulmonary disease, chronic heart failure, chronic renal failure, chronic liver failure, rheumatoid arthritis and AIDS. Whilst starvation leads to depletion in both fat mass and lean body mass, cachectic patients often suffer disproportionate loss of skeletal muscle mass. Loss of muscle mass in elderly does not necessarily occur with certain disease, and this is coined sarcopenia.

How common is cancer cachexia?

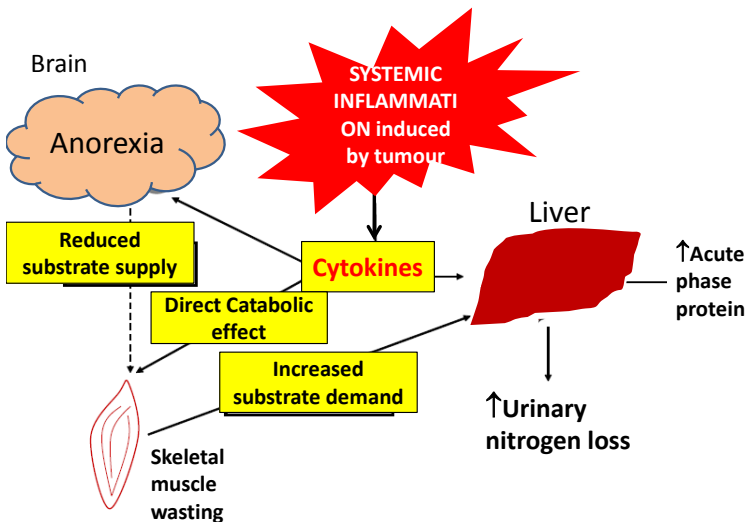
Cancer-induced cachexia (CIC) is experienced by up to 80% of patients with advanced stage cancer, particularly those with gastrointestinal, pancreatic, thoracic, and head and neck malignancies. CIC has been implicated in up to 20% of cancer-related deaths.⁽¹⁾

Weight loss is often noted as the first sign in cancer patients, being noted in 30% to 80% or more of the patients, and severe (by 10% or more) weight loss is observed in about 15% of the patients.⁽²⁾

In some cancer patients weight loss may be the most frequent presenting symptom, and up to 66% of patients develop inanition during the course of their disease. A weight loss greater than 10% of the preillness body weight may occur in up to 45% of hospitalized adult cancer patients.⁽³⁾

What are the underlying mechanism of cancer cachexia?

One of the main pathogenetic mechanisms underlying cancer cachexia is a complex interaction between the host and the tumour. Tumour cells interact with host cells within the tumour mass resulting in the production of catabolic mediators which degrade host tissue. In addition, the host may mount an aberrant metabolic response to the tumour. However, in recent years, it has also been understood that patient factors, including age and levels of physical activity, and the specific mechanics of protein metabolism in cancer patients may also have a significant impact.⁽⁴⁾ The excessive loss of skeletal muscle mass is due to the presence of a chronic inflammatory response perpetuated by proinflammatory cytokines (tumour necrosis factor (TNF)- α , interferon (IFN)- γ , interleukin (IL)-1 and IL-6) and stimulation of the neuroendocrine stress response. Other potential mediators of cachexia include deficiencies of anabolic factors (e.g. testosterone, insulin-like growth factor (IGF)-1) and an excess of catabolic factors (eg. myostatin, glucocorticoids).⁽⁵⁾



Schematic diagram from Skipworth⁽⁶⁾ Pro-inflammatory cytokines may induce muscle wasting either directly, or indirectly, via anorexia and generation of an acute phase protein response (APPR). During APPR,

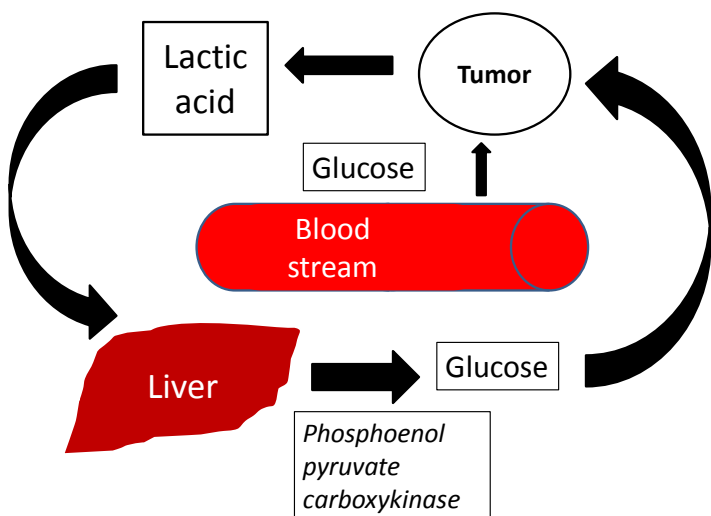
increased synthesis of hepatic protein (such as C-reactive protein puts an added demand on the bodys labile amino acid reserves, which is met, by the breakdown of skeletal muscle.

Why do cancer cells take up glucose much more than normal cells?

The most important concept to understand about tumor cells is that they require large amounts of glucose (as opposed to oxygen) to grow, usually four to five times the amount of glucose as compared to normal cells. Malignant tumors obtain 50% of their energy from glycolysis, thus keeping patients in a constant state of gluconeogenesis. Because oxygen is not utilized as much as glucose in tumor cells, when the tumor cell takes glucose, the glucose is converted into lactic acid. This lactic acid stimulates the liver to produce glucose via the enzyme phosphoenol pyruvate carboxykinase.
(7,8)

After receiving the newly synthesized glucose from the liver, the tumor produces lactic acid, which activates the liver to produce more glucose. This process is known as the Cori cycle, also referred to as the energy-wasting cycle.

The Cori cycle is hypothesized to be the mechanism by which any form of energy is depleted in patients with cancer due to the altered metabolism of carbohydrates because the cycle activity is increased by 50% in patients with cancer and accounts for 60% of lactate produced.



Does nutrition support stimulate tumor growth?

Parenteral nutrition (PN) is widely used in malnourished cancer patients who are candidates for major abdominal surgery. Numerous prospective, randomized trials have demonstrated that it effectively reduces postoperative complications. However, major concern about the use of PN in cancer patients still exists because nutrients administered to prevent or correct malnutrition in cancer patients might, at least theoretically, stimulate tumor proliferation.

A recent study suggests that PN does not stimulate tumor proliferation in malnourished patients affected by gastric cancer.⁽⁹⁾

What causes anorexia in cancer patients?

In this regard, tryptophan plays important role in the pathogenesis. Indeed, tryptophan crosses the blood–brain barrier by a specific transport mechanism shared

with the other neutral amino acids, including the branched-chain amino acids. Thus, by artificially increasing the plasma levels of the competing amino acids, a reduction of tryptophan brain entry could be achieved, leading to a reduction of hypothalamic serotonin synthesis and release, which in turn would result in amelioration of cancer anorexia. To test this hypothesis, anorectic cancer patients were orally supplemented with branched-chain amino acids or placebo for 7 d while recording their energy intake.

Anorexia significantly improved only in cancer patients receiving branched-chain amino acids, leading to a significant improvement of energy intake. These data are in agreement with previous observations in healthy individuals receiving total parenteral nutrition to induce anorexia, whose appetites were significantly improved when the parenteral mixture was enriched with branched-chain amino acids.⁽¹⁰⁾

What is the rationale of preoperative nutrition support in cancer patients?

1. Malnourished patients are at risk of postoperative complications.
2. Anorexia (ie., a reduced nutrient intake) often occurs in cancer patients and correlates with nutrition state and frequency of complications.
3. Although malnutrition usually develops as a chronic condition over several weeks or months, a short course of nutrition support can improve important physiologic functions.
4. Patients receiving preoperative nutrition support better tolerate postoperative TPN when glucose tolerance is reduced and enteral administration cannot meet all nutritional requirements.

Which is better for surgical cancer patients, parenteral nutrition or enteral nutrition?

Unless there is no contraindication of EN, it is preferable than PN.

Direct comparison between TPN and EN through randomized clinical studies has led to partly conflicting results, but only TPN showed some significant advantages with regard to weight gain, nitrogen balance, maintenance of serum albumin levels, and some mineral balances (potassium, magnesium, phosphorus, sodium, and chlorine). However, differences were marginal, and the slight advantage of TPN did not support its being used indiscriminately in malnourished cancer patients with a working gastrointestinal tract. Dresler et al demonstrated that only 32% of the parenterally infused nutrients are used for protein synthesis, as compared with 61% of oral intake. ⁽³⁾

Barlow et al ⁽¹¹⁾ studied one hundred and twenty-one patients with suspected operable upper gastrointestinal cancer (54 oesophageal, 38 gastric, 29 pancreatic) were studied. Patients were randomised to receive EEN (n = 64) or Control management postoperatively (nil by mouth and IV fluid, n = 57). Analysis was based on intention-to-treat and the primary outcome measure was length of hospital stay.

Results: Operative morbidity was less common after EEN (32.8%) than Control management (50.9%, $p = 0.044$), due to fewer wound infections ($p = 0.017$), chest infections ($p = 0.036$) and anastomotic leaks ($p = 0.055$). Median length of hospital stay was 16 days (IQ = 9) after EEN compared with 19 (IQ = 11) days after Control management ($p = 0.023$).

Conclusions: EEN was associated with significantly shortened length of hospital stay and improved clinical outcomes. These findings reinforce the potential benefit of early oral nutrition in principle and as championed within enhanced recovery after surgery programmes, and such strategies deserve further research in the arena of upper GI surgery.

Is there any new recommendation about nutrition requirement in surgical cancer patients?

A commonly accepted nutrition regimen would provide 30–35 kcal kg⁻¹ day⁻¹ and 1–2 g amino acids kg⁻¹ day⁻¹ with lipids making up 30–50% of the total energy content. ⁽¹²⁾

What about the role of immunonutrition in cancer cachexia?

Between January 2003 and December 2009, 305 malnourished patients (123 F, 182 M, mean Age 60.8) undergoing resection for pancreatic or gastric cancer, after preoperative 14 days of parenteral feeding, were randomized in double-blind manner to receive either postoperative immunomodulating enteral diet (IMEN) or standard oligopeptide diet (SEN).

Outcome measures of the intend-to-treat analysis were: number and type of complications, length of hospitalization, mortality, and vital organ function.

Results: Median postoperative hospital stay was 17.1 days in SEN and 13.1 days in IMEN group (p = 0.006). Infectious complications were observed in 60 patients (39.2%) in SEN and 43 (28.3%) in IMEN group (p = 0.04). Differences were also observed in overall morbidity (47.1 vs 33.5%, p = 0.01) and mortality (5.9 vs 1.3%, p = 0.03), but the ratio of surgical complications, organ function, and treatment tolerance did not differ.

Conclusions: The study proved that postoperative immunomodulating enteral nutrition should be the treatment of choice in malnourished surgical cancer patients. ⁽¹³⁾

Branched-chain amino acids have been known to increase appetite. Do they have any other role in cancer patients?

By using a crossover experimental design, Biolo et al compared the metabolic effects of isonitrogenous

solutions of balanced and branched-chain– enriched amino acid mixtures infused at the rate of 82 mg/kg/h for 3 h in patients with colorectal or cervical cancer on the first and second days after radical surgery combined with intraoperative radiation therapy. The ratios of leucine to total amino acid (grams) in the two mixtures were 0.09 and 0.22, respectively. Muscle protein and glutamine kinetics were determined by using stable isotope of amino acids and the leg arteriovenous balance technique. Glucose and insulin were continuously infused throughout the 2-d study to maintain near euglycemia.

Results: Rates of muscle protein synthesis and degradation were not significantly affected by the balanced amino acid infusion. In contrast, the isonitrogenous, branched-chain– enriched amino acid mixture accelerated muscle protein turnover by stimulating ($P \leq 0.05$) protein synthesis. The rate of muscle glutamine de novo synthesis did not significantly change after infusion of the balanced amino acid mixture but increased ($P \leq 0.05$) by $263 \pm 69\%$ during infusion of the branched-chain-enriched amino acid mixture.

Conclusions: An excess of branched-chain amino acids in the presence of an optimal profile of other essential amino acids acutely increased muscle protein synthesis and glutamine flux from skeletal muscle in cancer patients after surgery.⁽¹⁴⁾

References:

1. Gullett NP, Mazurak VC, Hebbar G, Ziegler TR. Nutritional Interventions for Cancer-Induced Cachexia. *Curr Probl Cancer* 2011;35:58-90.
2. Arends, J. et al. ESPEN Guidelines on Enteral Nutrition: Non-surgical oncology: *Clinical Nutrition* 2006; 25: 245-259
3. Bozzetti F. Rationale and Indications for Preoperative Feeding of Malnourished Surgical Cancer Patients. *Nutrition* 18:953–959, 2002

4. Richard J.E. Skipworth RJE. Pathophysiology of cancer cachexia: Much more than host–tumour interaction. *Clinical Nutrition* (2007) 26, 667–676
5. Stephens NA, Fearon KCH. Anorexia, cachexia and *Nutrition Medicine*, Volume 36, Issue 2, February 2008, Pages 78–81
6. Skipworth RJE et al. Pathophysiology of cancer anorexia: Much more than host–tumour interaction? *Clinical Nutrition* (2007) 26, 667–676
7. Amanda JT. The Biochemical Basis of Metabolism in Cancer Cachexia. [DIMENS CRIT CARE NURS. 2004;23(6):237–243
8. Leonardo M.R. Ferreira LMR. Cancer metabolism: The Warburg effect today *Experimental and Molecular Pathology* 89 (2010) 372–380
9. Pacelli F, et al. Parenteral Nutrition Does Not Stimulate Tumor Proliferation in Malnourished Gastric Cancer Patients. *JPEN J Parenter Enteral Nutr* 2007 31: 451
10. Laviano AL et al. Neurochemical Mechanisms for Cancer Anorexia. *Nutrition* 18:100 –105, 2002
11. Barlow R et al. Prospective multicentre randomised controlled trial of early enteral nutrition for patients undergoing major upper gastrointestinal surgical resection. *Clinical Nutrition* xxx (2011) 1- 7
12. Bozzetti F. Basics in Clinical Nutrition: Nutritional support in cancer–SPEN, the European e-Journal of Clinical Nutrition and Metabolism 5 (2010) e148–e152
13. Klek S. The immunomodulating enteral nutrition in malnourished surgical Patients. *Clinical Nutrition* 30 (2011) 282e288
14. Biolo G et al. Response of muscle protein and glutamine kinetics to branched-chain– enriched amino acids in intensive care patients after radical cancer surgery. *Nutrition* 22 (2006) 475–482

SARCOPENIA

Budhi Santoso

Introduction

Chronic diseases as well as aging are frequently associated with deterioration of nutritional status, loss muscle mass and function (i.e. sarcopenia), impaired quality of life and increased risk for morbidity and mortality ⁽¹⁾. The prevalence of clinically significant sarcopenia is estimated to range from 8.8% in young old women to 17.5% in old men ⁽²⁾. This occurs to a greater extent in men than women and persons who are obese and sarcopenic (the “fat frail”) have worse outcomes than those who are sarcopenic and non-obese ⁽³⁾. Mechanisms that underlie this process are beginning to be understood ⁽⁴⁾.

Definition

Sarcopenia is a term utilized to define the loss of muscle mass and strength that occurs with aging ⁽²⁾. The importance of defining the distinction lies in developing a targeted therapeutic approach to skeletal muscle loss and muscle strength in older persons. Failure to distinguish among these causes of skeletal muscle loss often results in frustration over the clinical response to therapeutic interventions.

Pathogenesis

- a) Sarcopenia physiologically caused by anorexia of aging is caused in part by alterations of stomach-fundus compliance and release and activity of cholecystokinin ⁽⁵⁾.
- b) There is evidence of an age-related decrease in the synthesis rate of myosin heavy chain proteins, the major anabolic protein. Motor units innervating muscle decline with aging, and there is increased irregularity of muscle unit firing ⁽⁴⁾.
- c) There are indications that cytokines especially interleukin-1, tumor necrosis factor, and interleukin-6 play a role in

the pathogenesis of sarcopenia, thus accelerating the development of frailty in older persons. Numerous treatable causes of anorexia and weight loss exist ⁽⁵⁾.

- d) The decline in anabolic hormones, namely, testosterone, dehydroepiandrosterone growth hormone, and insulin-like growth factor-I is also implicated in the sarcopenic process. The role of the physiologic anorexia of aging remains to be determined ⁽⁵⁾.
- e) Depression is the most commonly diagnosed cause of pathologic weight loss in older persons.
- f) Age-related cardiac sarcopenia occurs in mice and that LV remodeling due to increased end diastolic pressure could be an underlying mechanism for age-related LV dysfunction ⁽⁶⁾.
- g) Furthermore, increased levels of apoptosis have also been reported in old rats undergoing acute muscle atrophy subsequent to muscle unloading, a condition that mimics the muscle loss observed during prolonged bed rest. Notably, preliminary evidence seems to confirm a causative role for apoptosis in age related muscle loss in human subjects ⁽⁷⁾.

Diagnosis

Diagnosis of sarcopenia is based on the combined presence of the two following criteria ⁽¹⁾:

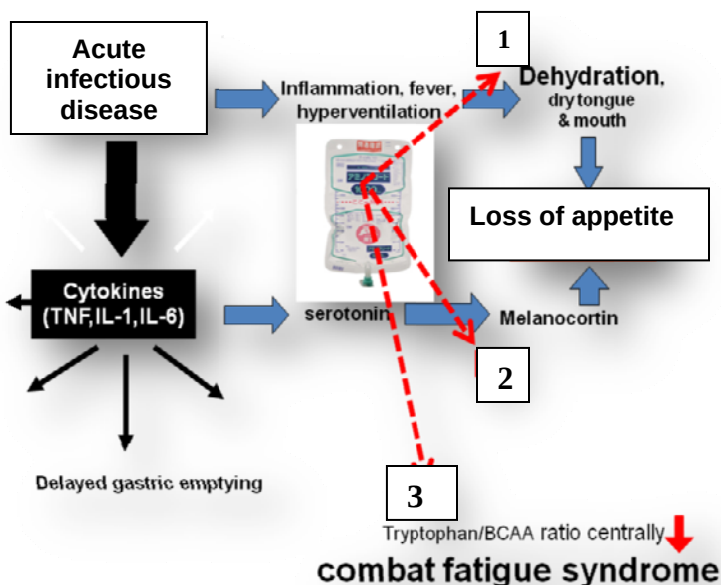
- a) A low muscle mass, i.e. a percentage of muscle mass 2 standard deviations below the mean measured in young adults of the same sex and ethnic background. Subjects aged 18–39 years in the 3rd NHANES population might be used as reference. The suggested T-score-based diagnosis of sarcopenia relates closely to the diagnosis of osteoporosis.
- b) Low gait speed, e.g. a walking speed below 0.8 m/s in the 4-m walking test.

5. Treatment

- a) The poor appetite and weight loss that occur in many frail individuals are likely to be accompanied by a degree of visceral protein depletion (with its attendant morbidity) ⁽¹⁾.
- b) The role of decreased anabolic hormone production in causing these changes remains to be clearly defined. Anabolic hormone replacement is a potential strategy

currently being investigated for treatment of sarcopenia. Combinations of aerobic, resistance, and stretching exercise programs have well established beneficial effects. Further understanding of the molecular processes involved in the aging of muscle both at the level of gene expression and protein modification will be important for discovering novel treatment strategies ⁽³⁾.

- c) Patients hospitalized with sarcopenia and indicated infusion therapy must considered cautiously with rational maintenance fluid which not just avoiding dehydration but also could decrease anorexia and combating fatigue as well. PT Otsuka Indonesia already launch the new trend in maintenance fluid therapy called “Aminofluid®” with double chamber soft bags and 3 in 1 benefits for treating dehydration, anorexia and combating fatigue ⁽⁸⁾ (see the diagram below):



References

1. Brass EP, Sietsema KE. Considerations in the Development of Drugs to Treat Sarcopenia J Am Geriatr Soc 59:530–535,

2. Morley, John E, et al; Sarcopenia (from the Chicago Meetings); J Lab Clin Med 2001;137:231-43.
3. Moerley, John E, BCh; Anorexia, Sarcopenia, and Aging; Nutrition, 2001; 17:660–663. ©Elsevier Science Inc. 200
4. Greenlund, LJS; Nair, K.S. Nair Department of Endocrinology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA
5. Edström, Erik, et all; Factors contributing to neuromuscular impairment and sarcopenia during aging; Karolinska Institutet, Department of Neuroscience, Retzius Laboratory, S-171 77 Stockholm, Sweden; Physiology & Behavior 92 (2007) 129–135.
6. Lin, Jing A, et all; Age-related cardiac muscle sarcopenia: Combining experimental and mathematical modeling to identify mechanisms. Experimental Gerontology 43 (2008) 296–306
7. Marzetti, Emanuele; Leeuwenburgh, A; Skeletal muscle apoptosis, sarcopenia and frailty at old age; Experimental Gerontology 41 (2006) 1234–1238

NUTRITIONAL SUPPORT IN SEPTIC PATIENTS

Budhi Santoso

Introduction

Sepsis refers to a bacterial infection in the bloodstream or body tissues. This is a very broad term covering the presence of many types of microscopic disease causing organisms. Sepsis is usually treated in the intensive care unit with intravenous fluids and antibiotics. **Severe sepsis** occurs when sepsis leads to organ dysfunction, low blood pressure (hypotension), or insufficient blood flow (hypoperfusion) to one or more organs (causing, for example, lactic acidosis, decreased urine production, or altered mental status). Sepsis can lead to septic shock, multiple organ dysfunction syndrome (formerly known as multiple organ failure), and death. Organ dysfunction results from **sepsis-induced hypotension** (< 90 mmHg or a reduction of ≥ 40 mmHg from baseline) and diffuse intravascular coagulation, among other things ⁽¹⁾.

Metabolic Response

The metabolic response to injury and sepsis has been well studied and characterized by increased resting energy expenditure, extensive protein and fat catabolism, negative nitrogen balance, hyperglycemia, and increased hepatic glucose production (pioneering work of Cuthbertson, Moore, and Kinney), Cuthbertson originally described the metabolic response to injury in three phases: ⁽²⁾

1. The ebb or early shock phase of decreased metabolism.
2. The flow or catabolic phase.
3. The convalescent or anabolic phase when re-synthesis of lost tissue can take place.

Neuroendocrine Response

The neuroendocrine response to injury results in a rise in the secretion of the catabolic hormones cortisol, glucagon and catecholamines with insulin resistance, resulting in a diversion of substrates from non-essential tasks to those necessary for healing. In summaries these neuroendocrine stress response, will induces: ⁽³⁾

1. Gluconeogenesis
2. Mobilisation of substrates glucose/glutamine/fatty acids
3. Proteolysis in peripheral tissues and negative nitrogen balance
4. Increased REE
5. Fluid retention
6. Insulin and GH resistance

Nutritional Support

Nutritional support in the intensive care setting represents a challenge but it is fortunate that its delivery and monitoring can be followed closely. Enteral feeding guidelines have shown the evidence in favor of early delivery and the efficacy of use of the gastrointestinal tract. Parenteral nutrition (PN) represents an alternative or additional approach when other routes are not succeeding (not necessarily having failed completely) or when it is not possible or would be unsafe to use other routes. The main goal of PN is to deliver a nutrient mixture closely related to requirements safely and to avoid complications.

Best Timing

No study has evaluated the best timing for PN initiation in ICU patients. Nevertheless, the European (ESPEN) and Canadian (CSCN) clinical guidelines recommend the initiation of EN within 24 h or 24–48 h, respectively, after admission to ICU. By extension, PN, if indicated,

should also be initiated within 24–48 h after ICU admission since it has been demonstrated that it does not increase mortality in comparison with EN. ⁽⁴⁾

Recommended daily substrate intakes in critical illness.

	Minimum dosage g/kg/day	Maximum dosage g/kg/day	Remark
Glucose	2	6	Give insulin if necessary
Fat emulsion	0.5	1.5	Recommend MCT/LCT
Amino acids	1.2	2.0	Special Formula: high BCAA

Espen recommendation ⁽⁴⁾ :

1. The minimal amount of carbohydrate required is about 2 g/kg of glucose per day
2. When PN is indicated, a balanced amino acid mixture should be infused at approximately 1.3–1.5 g/kg ideal body weight per day, in conjunction with an adequate energy supply
3. When PN is indicated in ICU patients the amino acid solution should contain 0.2–0.4 g/kg/day of L-glutamine
4. Intravenous lipid emulsions (LCT, MCT or mixed emulsions) can be administered safely at a rate of 0.7 g/kg up to 1.5 g/kg over 12–24 h
5. Critically ill patients are prone to fluid and sodium overload, and renal dysfunction is frequent. Therefore it is neither adequate nor appropriate to propose guidelines for the use of electrolytes on the basis of body weight or as a fixed element of parenteral nutrition. The highly variable requirements should instead be determined by plasma electrolyte monitoring.
6. All PN prescriptions should include a daily dose of multivitamins and of trace elements.

Using Immunonutrition⁽⁵⁾

Nevertheless, the development of immunonutrition (IMN), a special form of enteral feed supplemented with specific nutrients (omega-3 fatty acids, arginine, nucleotides and sometimes glutamine) has demonstrated a beneficial effect on patients' immune systems. The advantages of IMN have been demonstrated in a number of studies. Two recent meta-analyses have concluded that the use of IMN results in a significant reduction in infection rates, and as a consequence, shorter durations of hospital stay.

Permissive Underfeeding on Septic Patients

Base on current energy estimated, the recommendation for total calories intake: 25 to 30 kcal/BW/day and protein intake: 1 to 1.5 g/BW/day. There were no data regarding the benefit of fulfilling calories measured by indirect calorimetry. And some study considered giving nutrition beyond energy requirement will exacerbate the infections process and increasing the mortality of the patient relevant to septic. Even though when giving the full nutrition will support our body growth and protein metabolism, there was a negative effect, such increasing: bacteria virulent, cytokine release, infectious process and energy consumption of our body. This finding bring us to the permissive underfeeding concept.

There was prospective RCT which enrolled 40 hospitalized patients which giving the hypocaloric PN (1000 kcal/day and 70 grams protein/day) compare to standard PN (25 kca/kgBW/day and 1.5 gram protein/kgBW/day), and after negative nitrogen balance parameters measured there was no significantly different result between these two groups interm of non infectious complication rate, prolonged hospitalization and mortality rate. But in PN Standard group the data shows the infectious rate was increased (11 from 20 versus 7 from 20 in hypocaloric groups). So, until there was a new

adequate recommendation define toward, it was logically approached to give NPC 20 kcal/kgBW/day and protein intake 1 g/kgBW/day in hospitalized septic patients ⁽⁷⁾

References:

1. Dellinger RP, Levy MM, Carlet JM, et al., for the International Surviving Sepsis Campaign Guidelines Committee. (2008). "Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2008" (Subscription required). *Crit Care Med* **36** (1): 296–327.
2. Chiolerio, Rene MD; Revelly, JP MD; Tappy, Luc; Intensive Care Unit, Department of Anaesthesiology, Centre Hospitalier Universitaire Vaudois (CHUV); Lausanne, Switzerland Nutrition 1997;13(Suppl):45S-51S.
3. Hammarqvist, Folke; Wernerman, Jan; Allison, Simon; Basics in clinical nutrition: Injury and sepsis – The neuroendocrine response; Karolinska University Hospital Huddinge, Stockholm, Sweden; The European e-Journal of Clinical Nutrition and Metabolism 4 (2009) e4–e6.
4. Singer, Pierre, et al [a](#), ESPEN Guidelines on Parenteral Nutrition; *Clinical Nutrition* 28 (2009) 387–400.
5. Coates, Elizabeth, BA; A cost-effectiveness study of enteral immune modulating nutrition in intensive care patients; Sheffield (MERCs) Intensive Care Unit Royal Hallamshire Hospital Glossop Road Sheffield S10 2JF United Kingdom
6. Zaloga GP, Roberts P: Permissive underfeeding. *New Horiz* 1994;2:257-263.
7. Marik PE. Nutritional Support in Patients with Sepsis. In Rolandelli RH: Enteral and Tube Feeding. Elseviers Saunders. 2005;373-380

NUTRITIONAL SUPPORT IN CHRONIC RENAL FAILURE

Budhi Santoso

Nutritional support in patient with chronic renal failure can be problematic. The metabolic side effect in the body of the Chronic Renal Failure (CRF) patient has already been known and difficult to treat. Consider 3 main basics of pathophysiology: the patient conditions themselves (dialysis or not), nutritional status and inadequate oral intake ⁽¹⁾.

Patients on hemodialysis still have risk of malnutrition ⁽²⁾, because of:

1. Anorexia – reduced oral nutrient intake
2. Gastrointestinal consequences of uremia
3. Restrictive diets
4. Uremic toxicity – inadequate dialysis prescription
5. Metabolic acidosis
6. Endocrine factors (PTH, insulin resistance etc.)
7. Dialysis-associated factors (loss of nutrients, induction of protein catabolism)
8. Intercurrent disease (infections, etc.)

Historically, the use of low-protein and very low-protein diets had improved the anthropometric and biochemical parameters in non-dialysis patients but in patients with renal failure under dialysis, the studies reviewed do not support the prescription of a very low-protein diet with the aim of reducing the nutritional status of the patients.

Furthermore, controversy regarding the timing to initiate the daily protein adjustment in CRF patient will arise because they are not similar with other hospitalized moderate catabolic patients (1.5 g/kgBW/day). Giving such protein dose in CRF patients could increase end nitrogen product which results in decreased excretory function of the kidney. Otherwise, low protein strict diet will bring negative balance nitrogen causing serious

metabolic hazard in the body and finally increasing the complications and mortality rate of the CRF patients themselves⁽³⁾.

It is why conducting nutritional support in CRF patients becomes important and must adequately meet the goal of nutritional support in CRF like maintaining the nutritional status of the patient even to increase it better which automatically increasing the quality of life of the CRF patients.

Therefore, relevant studies were elaborated regarding the correlation between nutritional support in CRF Patients, as mentioned below :

1. Nutritional disorder in CRF patients basically results from the following mechanism⁽²⁾⁽⁴⁾:
 - Semi-starvation by drugs causing anorexia, dialysis, inadequate dialysis, socioeconomic, and other toxic metabolite products
 - Systemic inflammatory response (SIRS) which causes mobilization of catecholamine, glucagon and growth hormone which highly use the muscle energy such glucose and amino acids.
2. Patients with chronic renal insufficiency but without concurrent disease are at a high risk of malnutrition due to uremia associated factors, metabolic acidosis, impaired appetite and oral food intake and the gastrointestinal side effect of uremia. The main purpose of nutritional management are⁽²⁾⁽⁵⁾:
 - to prevent malnutrition
 - to reduce or control the accumulation of waste products
 - to prevent bone and cardiovascular disease
3. Muscle wasting and weakness are a common clinical feature in people with CRF and these data bring us to understand the kidney plays a major role in amino acid and protein metabolism and a pivotal role in producing tyrosine in the body and is the major contributor of tyrosine to the systemic circulation, thus maintaining the remodeling processes of the body⁽⁴⁾.

4. With a planned dietary regimen, severe or overt malnutrition does not occur in predialysis CRF without other serious illnesses ⁽⁵⁾.
5. Daily requirement recommendation by ESPEN regarding nutritional support in CRF as below table ⁽²⁾ :

Table Daily nutritional requirements in (stable) patients with CRF, on HD or CAPD.

	Conservative therapy	Hemodialysis	Peritoneal dialysis
Energy (kcal/kgBB)	>35	>35	>35 ^a
Protein (g/kgBB)	0.6–1.0	1.1–1.4	1.2–1.5
Phosphorus(mg) (mmol)	600–1000 19-31	800–1000 25-32	800–1000 25-32
Potassium (mg) (mmol)	1500–2000 ^b 38–40	2000–2500 40–63	2000–2500 40-63
Sodium (mg) (mmol)	1.8–2.5 ^b 77-106	1.8–2.5 77-106	1.8–2.5 77-106
Water(ml)	Unrestricted	1000 ml +DO	1000 ml+UF+DO

Note: **DO:** *daily (urine) output.*

a : *Included energy (glucose) from the dialysate.*

b : *Individual requirements can differ considerably.*

6. There were historical data regarding the beneficial used of amino acids in CRF patients as listed below ⁽⁸⁾:
 - Bergstrom J, et al (1972): extrapolated a significant data using intravenous nutrition with amino acid solutions in patients with chronic uremia.
 - Than Weinberg, et all (1987): The rational approach to nutritional therapy in patients with renal failure would be a combination of EAA & NEAA. Use of branch-chained amino acids is also beneficial.
 - Taraoka S et al (1990): reported hyperammonemia + orotic acidemia in uremic rats receiving TPN (arginine-freeEAA solution)
 - Than by Nakasaki H (1993). reported 6 cases of hyperammonemia and changes of mental status that developed during TPN composed of EAA and histidine

7. Kidmin[®] meets current recommendation as balanced amino acid infusion for renal failure patients⁽¹⁾:
 - Combination of EAA & Non-EAA (2.6 : 1)
 - High concentration of BCAA (45.8%)
 - Contains non-EAA (such as arginine) which prevent hyperammonemia due to urea cycle dysfunction and do not contain Glycine
8. Kidmin[®] also reported increased significantly the nutritional status (multicenter study) of CRF patients (increased total protein, albumin, prealbumin and transferin)

References:

1. Roesli, Rully; The First Jakarta Nephrology Hypertension Course; Sub.Bag Ginjal Hipertensi, Bagian Ilmu Penyakit Dalam Fakultas Kedokteran Unpad, Jakarta, 2001.
2. Druml, W; in Clinical Nutrition: Nutritional support in renal disease; University of Vienna and Vienna General Hospital, Vienna, Austria Basics; e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism 5 (2010) e54–e57
3. Zarazaga, A; et all; Nutritional support in chronic renal failure: systematic review; Clinical Nutrition (2001) 20(4): 291±299
4. K. Sreekumaran Nair, MD, PhD, Mayo Clinic College of Medicine, Journal of Renal Nutrition, Vol 15, No 1 (January), 2005: pp 28-33
5. Cupisti, Adamaso, MD, et all; Nutritional Status and Dietary Manipulation in Predialysis Chronic Renal Failure; Journal of Renal Nutrition, Vol 14, No 3 (July), 2004: pp 127-133
6. Ota K et al. Nutritional Management of Chronic Renal Failure Patients by TPN Japanese Journal of Parenteral and Enteral Nutrition 1993;15:1043-1059
7. Ota K; Multicentre Comparative Study. Japan Journal of Parenteral and Enteral Nutrition 1993;11:1226-1251
8. Hensley MK. Historical Perspective of Nutrition in Kidney Disease Nutrition and Health, 2008, Nutrition in Kidney Disease, Part I, Pages 17-33

NUTRITIONAL THERAPY IN BURN PATIENTS

Budhi Santoso

Introduction

Assessing the effective nutritional therapy in burn patients involves an understanding of the physiologic and metabolic alterations that accompany traumatic injury. Advances in infection control, early excision and grafting and aggressive nutritional support have greatly improved survival from severe burn injury. Nutritional support must also accommodate the surgical and medical needs of the patient.⁽¹⁾ Furthermore, the following steps were considered in assessing the nutritional support in burn patients:

- Determining nutritional status and nutrition risk
- Evaluating nutritional adequacy
- Determination of energy and protein requirements, including: Metabolic factors that influence macronutrient utilization, Clinical factors that influence energy requirement, using Indirect calorimetry and Estimation of protein needs.

Extensive burns elicit a pronounced metabolic response causing physiological derangements leading to the hyper-metabolic state. The hyper-metabolic response is accompanied by severe catabolism and a loss of lean body mass and also by a progressive decline of host defenses that impairs the immunological response.⁽²⁾

Evidence indicated some of the pathophysiological response such as negative muscle protein net balance, insulin resistance, loss of bone mineral content and increased heart rate may continue until 24 months and even longer.⁽³⁾ The Resting Energy Expenditure (REE) of patient changes over time, with a peak lasting 2–6 weeks depending on burn severity and on complications. As both underfeeding and overfeeding do have

deleterious consequences, accurate assessment of REE is desirable to adjust the individual caloric intake, particularly in patients with a prolonged and complicated course: in severely burned patients the access to indirect calorimetric determination or REE is recommended. Giving enteral nutrition is still the first choice, but may be supplemented by PN if nutrient intake is inadequate. Burned patients have increased trace element losses, which contribute to delayed recovery. Weight changes and energy intakes should be monitored daily.

Energy requirement

Energy requirements vary over time, with the largest increases being observed during the first weeks after injury. In a series of burned and injured patients, described by Larsson et al (1984) given 45–50 kcal/kgBW/day energy intake (high by modern standards). According to modern literature, the REE in burned patients ranges from 1.3 to 1.5 times that estimated from the Harris–Benedict equation although, occasionally, slightly higher figures may occur. ⁽⁴⁾

Estimation of protein needs

Severe burn is characterized by increased amino acid efflux from the skeletal muscle of the body presumably to accommodate amino acid needs for:

- tissue repair,
- acute-phase protein production,
- cellular immunity,
- and gluconeogenesis.

A nitrogen balance improved up to a protein intake of 0.2 g kgBW/day to 1.25 g kgBW/day (2–3 times the minimum requirement for normal subjects) and the current practice (Europe) is to give 1.3–1.5 g protein/kgBW/day (0.2–0.25 g N/kgBW/day) ⁽⁴⁾

The enteral route

Enteral nutrition is preferred in burns as in other critically ill patients. Early enteral administration of nutrients can improve splanchnic perfusion (animal trials), blunt the hypermetabolic response, stimulate intestinal IgA production and maintain intestinal mucosal integrity. By the end of the first week after injury most of the patient's energy requirements should be supplied enterally.⁽⁴⁾ Diarrhoea is a frequent complication of tube feeding. The causes of this complication are several, including antibiotics, excessive rate of administration of hyperosmolar feeds, etc. If nutritional requirements are not met using the enteral route, parenteral supplementary feeding may be given. In critically ill patients there is consistent evidence that significant benefits are achieved if nutrients are delivered within the gut compared with the parenteral route. However, in conditions related to gut hypoflux, enteral nutrition may play a double role in counterbalancing the installed low-flow state.⁽⁵⁾ The use of early naso-gastric tube insertion, charting out daily calorie intake and using low cost feeds consistent with local dietary habits lead to a significant decrease in average number of days and the number of procedures in 20–39% TBSA burns; and caused the significant decrease in mortality, average number of days and the number of procedure in 40–59%TBSA burns.⁽²⁾

Nutrition support strategies

Once energy and protein requirements are established, the mode of nutrient delivery that best meets both the metabolic and clinical needs of the patient is determined.

Glutamine

Glutamine is considered important in many disease states for its numerous properties. With two amine groups, it functions as a nitrogen shuttle, carrying

nitrogen for purine and pyrimidine synthesis. Glutamine serves as a primary oxidative fuel source for rapidly dividing cells, including the enterocyte. As a precursor to glutathione, a potent antioxidant, glutamine participates in reducing oxidative damage.⁽⁶⁾ Glutamine supplementation in burn injury has shown moderate benefit. We studied the effect of glutamine supplementation (0.6 g/kg) on protein economy and found that a glutamine-enriched diet had a similar effect on protein turnover and breakdown as a mixture of essential amino acids.⁽⁷⁾ In another study, glutamine supplementation resulted in decreased muscle protein breakdown (as indicated by 3-methyl-histidine) and improved wound healing when fed enterally.

Arginine

Stress-induced depletion of arginine in tissue pools suggests that it too is semi-essential after burn. Increased extrahepatic uptake of arginine contributes to accelerated urea production in burn patients further exacerbating its losses from the body.⁽⁸⁾ This is concerning given arginine's role in wound healing (as a stimulant to growth hormone) and immunity through the nitric oxide pathway.⁽⁹⁾

Micronutrient

Evidence-based practice guidelines are currently unavailable for the assessment and provision of micronutrients in burn patients. Intuitively, diminished gastrointestinal absorption, increased urinary losses, altered distribution, and altered carrier protein concentrations following severe burn will lead to a deficiency in many micronutrients if not supplemented.

Nutrient supplementation protocol in children^a

Micronutrient	Enteral supplementation ^b	Parenteral Supplementation
Multivitamin with trace elements ^c	1 tablet/	1 vial dosis tunggal/day
Zinc ^d	25 mg/day	50 mg/kg/day
Copper ^d	2.5 mg/day	20 mg/kg/day
Selenium	50–170 mg/day	2 mg/kg/day
Vitamin C	2 mg/kg/day	200 mg/kg/day

- a Children greater than 3 years of age.
- b Children receiving adult or specialty formulas designed for wound healing may not require additional supplementation of individual nutrients.
- c Vitamins A, E, iron, B complex are provided only as part of multivitamin/trace element preparation.
- d Addition of a multivitamin supplement with trace elements may be sufficient for meeting requirements.

Formula selection

Historically, and to date, enteral supplements have been used to maintain nutritional status and divert negative outcomes associated with malnutrition. In this sense, standard polymeric feedings remain common practice in severe burns and are likely to be sufficient for supporting wound healing and lean body mass when energy and protein intakes are sufficient. Most specialty formulas that are of interest in burn nutrition have wound healing and/or immune enhancing properties. Study data regarding the beneficial used of Using the immune enhanced formula are listed below:

- A mechanism for enterally stimulated mucosal immunity involves selective perfusion of the terminal ileum during Immune Enhanced enteral Diets (IED) nutrient absorption, blood flow distribution depends on nutrient composition and that IED preferentially augments blood flow to the ileum.⁽¹⁰⁾

- The recommendation using IED for burn patient with TBS $\geq$ 30% (level 3) because significantly indicated reducing: the hospitalized and ICU length of stay, time of used antibiotics, time of used ventilator and prevalence of MOS. ⁽¹¹⁾

Neomune[®] is one of a nutritional complete formula with immune enhancing nutrient for tube and oral feeding and also already had been studied:

- Thailand by Prof. Dr. Chomchark et al, in Injured patients: Trauma 16 cases and burn 20 cases). The result significantly indicated feeding of Neomune[®] in these critically injured patients was well tolerated, shorten ICU stay and wean-off respirator day ⁽¹²⁾
- Indonesia (Sint. Carolus Hospital of Jakarta) by dr. Benny Philippi, et al in Post Operative Digestive Cancer Patients. The result indicated no major complications and no infectious complications in group of patients which using Neomune[®] ⁽¹³⁾

Neomune[®] contains: ⁽¹⁴⁾

- CHO: 25.01 g (Fructose + Maltodextrin combination) has many advantage over glucose polymer singly with regards to ease of digestion.
- Fat: 5.79 g (MCT + Omega3-Fish Oil + Corn Oil), numerous study indicated omega-3 fish oil has suppressive action and improve cell-mediated immunity
- Protein: 12.5 g (Casein + Arginine + Glutamine):
 - Casein has definite as whole protein because its low osmolarity, good taste and well digested.
 - Glutamine has important role to maintenance intestinal metabolism, structure and function
 - Arginine has been shown to decrease nitrogen losses and improve rate of wound healing

- Fiber (+) for maintain the gut peristaltic and combat constipation.
- Free lactose, could eliminates diarrhea and other side effect associated with lactose intolerance
- Level of multivitamins and minerals appropriate for patients receiving adequate calories
- Total Calorie: 200 kcal/sachet

References:

1. Prelack , Kathy, et all; Practical guidelines for nutritional management of burn injury and recovery; burns 33, 2007, p 14-24
2. P. Suri, Manaf; Nutrition in burns: Need for an aggressive dynamic approach; Burns 32, 2006: 880–884
3. Y. H. Chang, et al; Medical Nutrition Therapy for Pediatric Burn Patients after Discharged Home from Hospital; University of North Carolina Healthcare System, Chapel Hill, NC, USA, 2004
4. Berger, Meete; Basics in clinical nutrition: Nutritional support in burn patients Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
5. J. E. de Aguilar-Nascimento et al; Role of enteral nutrition and pharmaconutrients in conditions of splanchnic hypoperfusion; Nutrition 26 (2010) 354–358;
6. Martindale RG, Cresci GA. Use of immune-enhancing diets in burns. J Parenter Enteral Nutr 2001;25:S24–6.
7. Sheridan RL, Prelack K, Yu YM, et al. Short-term enteral glutamine does not enhance protein accretion in burned children: a stable isotope study. Surgery 2004;135:671–8.
8. Yu YM, Young VR, Castillo L, et al. Plasma arginine and leucine kinetics and urea production rates in burn patients. Metabolism 1995;44:659–66.
9. Dent DL, Heyland DK, Levy H. Immunonutrition may increase mortality in critically ill patients with pneumonia: results of a randomized trial. Crit Care Med 2003;30:17–20.
10. Rhoden, D et al; Immune-enhancing enteral diet selectively augments ileal blood flow in the rat.J Surg Res. 2002 Jul;106(1):25-30
11. Proceedings from Summit on Immune-Enhancing Enteral Therapy, San Diego, California. JPEN 25 (2), Suppl. 2000

12. Chunsatrakul, Chomcark, et al; Effects of Neo-Mune on Outcome in Severe Injury; Siriraj Hospital, Bangkok, 1996.
13. Philippi, B, et al; The Use of Immune-Enhancing Enteral Formula with L-arginine, L-glutamine, Omega-3 Fatty Acids for Post Operative Digestive Cancer Patients; St Carolus Hospital, Jakarta Indonesia MIMS annual, 20th edition, 2010, p.335
14. Neomune. Full Prescribing Information. MIMS.com

12. Chunsatrakul, Chomcark, et al; Effects of Neo-Mune on Outcome in Severe Injury; Siriraj Hospital, Bangkok, 1996.
13. Philippi, B, et al; The Use of Immune-Enhancing Enteral Formula with L-arginine, L-glutamine, Omega-3 Fatty Acids for Post Operative Digestive Cancer Patients; St Carolus Hospital, Jakarta Indonesia MIMS annual, 20th edition, 2010, p.335

INDEX

Acetated Ringer's,32,33,34,36,37,43,45,50,51,53
Acidosis,31,32,25,36,40,43,47-49,76,78,134,150
ADH (antidiuretic hormone),62,86,90,93,94,141
Albumin,25,26,52,90,133,166,186,203,207,266,291
Alkalosis,77,78,82,83,85,159,161,166
Aminofluid,117-119,123-125,131,136,138,152
ARDS,16,20,48
Arginine,61,64,86,95,115,129,130,266
Asering,15,27,33,39,40,45,47,49,54,55
ASPEN guideline,118,125,138,146,163,169
Bartter's syndrome,82,83,85
BCAA,144,163,165,168,187,188
Body Mass Index (BMI),116,283
Burns,44,120,165,219,223,308,310,312
Cachexia,125,169,286,287,292,
Cancer cachexia,286,287,292,294
Cancer,281,282,284
Central venous pressure (CVP),13
Chemotherapy,195,197,198,201,231
Colloid,20,23,24,25,50,137,161
Cori cycle,88
Crystalloid,20,25,26,31,40,43,45,157
CSWS(*cerebral sat wasting syndrome*),90,148
Cyclic infusion,227,228
Demeclocycline,91
Desmopressin,96
DHF,30,31,33,137,139
Diabetes insipidus,69,93,94,96
DKA, diabetic ketoacidosis,35,36,37
DSS (Dengue Shock Syndrome),32,33,43
Eclampsia,173,175
ESAS (Edmonton Symptom assessment system),180,181

ESPEN guidelines,146,209,285,293,300,301
 Extravasation,229-231
 Fatigue postoperative, 212
 Fatigue,131,132,139,144,162,170,178,181,182,184
 Fatigue,cancer-related,216
 Glutamine,120,130,144,165,189,266
 Head injury,113,114,274,275,276,279
 Hemoconcentration,30,137,270
 HES (Hydroxyethyl starch),24,26,50,51,52
 HOMA,249
 Hypercalcemia,198,199,200
 Hyperemesis gravidarum,166,167,185
 Hyperglycemia,157,158,166,205-207
 Hyperkalemia,79,124,198,201
 Hypernatremia,70,71,178,198
 Hypertonic saline,24,56,57,60,69,91,96
 Hypocalcemia,31,84,199,201
 Hypoglycemia,104,105,166,186,206
 Hypokalemia,76-81,84,96,116,124,153
 Hypomagnesemia,84,89,134,199
 Hyponatremia,31,56-60,65,66
 Hypophosphatemia,199
 Immunonutrition,266,268,269,292,302,314
 Infiltration,202,203,205,229,234
 Insulin resistance,134,136,143,144,153,
 KAEN,71,103,104,125,148
 Kidmin,307
 Lactated Ringer's,31,32,33,36,54,161,167
 Leucine,120,122,125,129,130,165,189
 Magnesium,83,84,112,133,135,136
 Maintenance fluid therapy115-117,124,125,136
 Malabsorption,133,135
 Malaria,severe,46
 Malnutrition,76,127,128,129,183,260,262

MAP,13,16,107,177
 Melanocortin,120,121,165
 Metabolic response,29,243,262,263,287,299,308
 Neomune,267,272,273,279,281,284,313
 NPY,121,122
 Nutrition,enteral,125,169,259,265,266,271,272,273,279
 Nutrition,parenteral,227,228,238,239,261,268
 Osmotherapy,106,109,110,111,112
 Pancreatitis,135,269,272,273
 Permissive underfeeding,268,302,303
 Phlebitis,123,179,202-204,219
 Postoperative fluid therapy,165
 Preeclampsia,101,167,173
 Protein-sparing effect,118,139,162,168,235,239
 Resuscitation,fluid,15,16
 SAFE Study,11-14,19,21,22,26
 Sarcopenia,283,286,295,296
 Sepsis,10,12,13,20,22,46
 Shock index,13
 Shock, 1
 Shock,compensated,3
 Shock,hemorrhagic,7,9,10,17,21,40,42
 Shock,hypovolemic,14,26,32,137,148,177
 Shock,septic 299,303
 SIADH,86-91
 Stroke,158,185,205,207,250,283
 Titratable acidity,226,228
 Tolvaptan,65,66,91,92
 Trauma,9,12,13-16,18,22
 Tryptophan,120,121,122,130,131,165,186
 Zinc,216,217,239,260

RESUSCITATION CRYSTALLOIDS

	CHO	Electrolytes (mEq/L)							
PRODUCTS	Glucose (gr/L)	Na ⁺	K ⁺	Ca ⁺⁺	Cl ⁻	Lactate	Acetate	(mOsm/L)	Vol (ml)
Ringer Solution	-	147	4	4,5	155,5	-	-	310	500 ml
Lactated Ringer's (LR)	-	130	4	3	109	28	-	273	500 ml
ASERING/ Acetated Ringer's (AR)	-	130	4	3	109	-	28	273	500 ml
ASERING-5	50	130	4	3	109	-	28	551	500 ml
RL-D5	50	130	4	3	109	28	-	551	500 ml
RD5	50	147	4	4,5	155,5	-	-	589	500 ml

APPENDIX: MAINTENANCE SOLUTIONS

PRODUCTS	CHO	Electrolytes (mEq/L)						(mOsm/L)	Vol (ml)
	Glucose (gr/L)	Na ⁺	K ⁺	Ca ⁺⁺	Cl ⁻	Lactate	Acetate		
Larutan 5% Glucose (BP)	50	-	-	-	-	-	-	278	1000 & 500
Larutan 20% Glucose (BP)	100	-	-	-	-	-	-	556	500 ml
NaCl 0,9%	-	154	-	-	154	-	-	308	500 ml
N/5-D10	100	31	-	-	31	-	-	615	500 ml
KAEN 1B	37,5	38,5	-	-	38,5	-	-	285	500 ml
KAEN 3A	27	60	10	-	50	20	-	290	500 ml
KAEN 3B	27	50	20	-	50	20	-	290	500 ml
KAEN MG3	100	50	20	-	50	20	-	695	500 ml
DGAA	25	61	17,5	-	52	26,5	-	296	500 ml
AMINOFLUID*	75	35	20	5	50	20	13	817	500 & 1000 ml

* Aminofluid also contains 30 g amino acids/L, microminerals (Mg⁺⁺, Ca⁺⁺, P) and zinc

PARENTERAL NUTRITION SOLUTIONS

PRODUCTS	CHO (g/L)	AA (g/L)	BCAA	Osmolarity (mOsm/L)	REMARKS
AMIPAREN	-	100	30%	911	Amino Acids for metabolic stress (eg sepsis, surgery), malnutrition
AMINOLEBAN	-	80	35.5%	768	For hepatic encephalopathy
KIDMIN		72	45.8%	608	Balanced Amino Acid solution for Renal Failure Patients
PAN-AMIN G	50	27.2	29%	507	provision of amino acid in the following clinical situations : Hypoproteinemia, malnutrition, or before or after surgery
AMINOVEL 600	50	100	17.6%	1145	As supplement nutrition in the case of the impairment of the gastrointestinal tract as in clinical situation of short bowel syndrome, anorexia and severe gastro-intestinal disorder
MARTOS	100	-	-	-	Maltose, provision of calorie in diabetes

CORRECTION FLUIDS

PRODUCTS	CHO	Electrolytes (mEq/L)						Vol (ml)
	Glucose (gr/L)	Na ⁺	K ⁺	Ca ⁺⁺	Cl ⁻		Acetate	
3% NaCl	-	513	-	-	-	-	-	500 ml
	CHO	Electrolytes (mEq/25 ml)						
PRODUCTS	Glucose (gr/mL)	Na ⁺	K ⁺	Mg ⁺⁺	Cl ⁻	SO ₄ ⁻⁻	HCO ₃ ⁻	Vol (ml)
							(mOsm/mL)	
20% NaCl	-	85,5	-	-	85,5	-	-	25 ml
7,46% KCL	-	-	25	-	25	-	-	25 ml
20% MgSO ₄	-			42	-	42	-	25 ml
40% MgSO ₄	-	-	-	83	-	83	-	25 ml
25% glucose	0,25	-	-	-	-	-	-	25 ml
40% glucose	0,4	-	-	-	-	-	-	25 ml
8,4% Meylon	-	25	-	-	-	-	25	25 ml

ABOUT THE AUTHORS



Dr Iyan Darmawan graduated from Andalas University School of Medicine in 1982, Padang. After a few years of clinical work he joined a leading medical publisher and some pharmaceutical companies and then showed interest in medical writing and translation. In 1994 & 1995 Dr Iyan attended advanced facilitation courses at Cambridge University, UK and became an accredited pharmaceutical trainer. He has spoken at various national and overseas symposia in the area of parenteral fluid therapy and clinical nutrition. Currently he is the Medical Director, CIBG Division of PT Otsuka Indonesia

Some related publication and translation work:

1. Martin, David W Jr et al: Biokimia David W. Martin Jr et al.. Ed 20, Jakarta, EGC, 1987
2. Nutrition in Chronic Liver Disease, Medical Progress March 1992.
3. English in Medicine, CD-ROM Farmedia 2004
4. Update on Sepsis, 2008 Farmedia
5. Kapita Selektta Hematologi, EGC 1986
6. Buku Ajar Nutrisi Bedah, 2000
7. Kedokteran Perioperatif, 2001
8. Fisiologi Asam-Basa, Stewart Approach, 2006
9. Manajemen Gangguan Elektrolit dan Asam-Basa 2002
10. Syok pada Anak, Farmedia 2009



Dr Budhi Santoso graduated from Medical Faculty of Brawijaya University, Malang, 1993. After some years of clinical work at Community Health Centre in Riau, he joined Schering AG as Medical Advisor and at present Dr Budhi is Senior Medical Advisor of PT Otsuka Indonesia. He has attended many postgraduate courses in Indonesia and abroad, including:

1. Advanced GCP course, Schering AG-Berlin, 1998
2. Communication on Family Planning, Sweden 1999
3. Nutrition Workshop, Tokushima, Japan, 2008
4. AUCOGS Congress, Philadelphia-USA, 2000
5. Schering internal leadership course, Dusit, Thailand, 2000
6. Critical Care Annual and Pensa Meeting: Bali 2002
7. ATLS advanced, RSCM 2003