Research Progress in Trauma Metabolism and Nutrition

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Abstract Trauma causes a series of alterations in body metabolisms, which may further aggravate organ dysfunction and lead to multiple organ failure (MOF). The typical metabolic responses to trauma can be summarized in six points: increased energy expenditure, accelerated gluconeogenesis, increased lipolysis, increased water-sodium retention, increased nitrogen excretion as well as decreased muscle protein synthesis. Nutrition support is critical in the management of trauma patients. The major functions of nutrition support are to prevent acute protein malnutrition, to modulate the immune response as well as to promote gastrointestinal structure and function. Despite the widespread use of nutrition in trauma patients, there still remains controversies in the aspect of the route and timing of nutrition support. In reviewing the literature studies concerning the route and timing of nutrition support in the trauma condition, we concluded that: First, enteral nutrition is superior to parenteral nutrition in critically ill trauma patients; Second, early enteral nutrition (within 24–48 h after admission to ICU) was more preferred compared with delayed enteral nutrition.

Keywords Trauma · Metabolic response · Nutrition support

1 General

Trauma causes abnormal manifestations in the body. These manifestations can cause alterations in body metabolisms including hypercatabolism, hyperglycemia, hypoalbuminemia, et al. These metabolic abnormalities may aggravate organ dysfunction and lead to multiple organ failure (MOF). In addition, these metabolic abnormalities may also complicate nutritional management.

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X. Fu and L. Liu (eds.), *Advanced Trauma and Surgery*,
DOI 10.1007/978-981-10-2425-2_10

2 Metabolic Response to Stress

Stress is a body's method of reacting to a challenge. According to the stressful event, the body's way to respond to stress is by sympathetic nervous system activation, which results in the fight-or-flight response [1]. Cannon first used the word "stress" to describe this fight-or-flight response. In the 1930s, Cuthbertson defined the ebb and flow of metabolic response after trauma [2]. A patient may undergo two phases during the time of stress: the ebb phase and the flow phase (Fig. 1).

The ebb phase, also named acute phase, usually lasts 1–3 days. The clinical presentation of ebb phase is hypometabolism, decreased temperature, decreased energy expenditure and normal glucose production, but with insulin resistance, mild protein catabolism, increased blood glucose, increased catecholamines, increased glucocorticoids, decreased cardiac output, lowered total oxygen consumption, and vasoconstriction. All these metabolic changes would lead to muscle catabolism.

The ebb phase ends after adequate resuscitation and replaced by the flow phase. The metabolic response of the flow phase is characterized by high oxygen consumption, hypermetabolism, increased resting energy expenditure (REE), increased cardiac output, increased glucose production, profound protein catabolism, increased catecholamines, increased glucocorticoids, increased glucagon, increased potassium, and increased nitrogen losses. During this phase, four types of mechanisms regulate metabolic changes: the release of tissue factors, the synthesis of cytokines, endocrine changes and central nervous system functions.

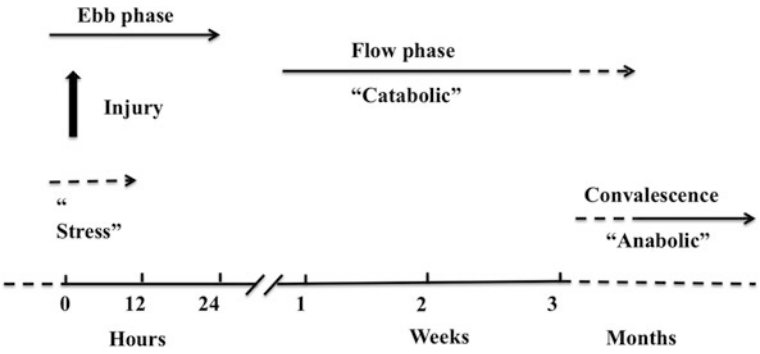

Fig. 1 Phases of the response to injury

3 Metabolic Response to Trauma

The typical metabolic response to trauma can be summarized in six points: increased energy expenditure, accelerated gluconeogenesis, increased lipolysis, increased water-sodium retention, increased nitrogen excretion as well as decreased muscle protein synthesis. The hypothalamus and the adrenergo-sympathetic system might play important roles in initiating these metabolic changes.

3.1 Increased Energy Expenditure

It has been shown that there is a moderate increase in the energy expenditure in patients after uncomplicated elective surgery. Only those patients with severe trauma, sepsis and burns would have a 50–100 % increase in energy expenditure. This increased energy demand can be met without problems by giving glucose and fat emulsions, but it may be necessary to measure the energy expenditure directly by indirect calorimetry in critically ill patients in order to prevent overloading of nutritional substrates, particularly in those with multiple organ failure (MOF).

3.2 Accelerated Gluconeogenesis

Hyperglycemia always follows injury. Hyperglycemia may be the result of rapid catecholamine-mediated mobilization of body carbohydrate stores in the early stage of trauma. The carbohydrate stores in the liver will last only 12–24 h without replenished. The body glucose requirement must be met with an increased hepatic production of glucose from protein precursors. While in the late stage, the hyperglycemia is always the result of an increased synthesis of glucose relative to an increased turnover rate. Injury and sepsis apparently do not impair the ability of the body to oxidize glucose, in turn, the glucose oxidation is actually increased in septic patients and gluconeogenesis cannot be suppressed even with intravenous glucose infusion. The study by Wilmore et al. [3] has demonstrated that wound is responsible for the increased glucose utilization instead of skeletal muscle.

3.3 Increased Lipolysis

The turnover rates of glycerol and free fatty acids are increased in postoperative patients, but the production of ketone bodies probably remains unchanged as skeletal muscle uses almost exclusively lipids as substrates.

3.4 Water-Sodium Retention

As is well known, trauma and sepsis would cause an increase in the muscle contents of water, sodium and chloride. Bergstrom et al. has revealed that, retained water is mainly distributed extracellularly in postoperative patients. Although potassium and magnesium are less affected, their concentrations in muscle are decreased after operation. And in the conditions of severe trauma and sepsis, these changes deteriorate more. For these reason, nutrition support may partly correct these water and electrolyte abnormalities.

3.5 Increased Nitrogen Excretion

Normally there is a balance between protein synthesis and breakdown, but the catabolic rate becomes much greater than synthetic rate in trauma patients. In most trauma patients, there is an increase in both synthesis and degradation. However, the enhancement of degradation is the more pronounced. As a result, the nitrogen balance becomes negative in the posttraumatic period. Skeletal muscle is the major source for the excreted nitrogen, leading to muscular fatigue and weakness. Therefore, it is very important to apply an appropriate nutrition formula to preserve the body proteins of the trauma patients. In addition to nutrition support, some adjuvant therapies such as insulin and growth hormone may also be necessary.

3.6 Decreased Muscle Protein Synthesis

O'Keefe et al. found that the total ribosome concentration per mg of deoxyribonucleic acid (DNA) and the proportion of polyribosomes decreased in postoperative patients, suggesting that the operative trauma would cause the decrease in ribosome utilization. The decrease in the concentration of polyribosomes is the same as that is observed during starvation, indicating that skeletal muscle is used as an important source of nutrients in trauma patients. Tissue analysis reveals a markedly decrease both in the activity of and the capacity for protein synthesis.

4 Nutrition Support in Trauma Patients

4.1 Rationale for Nutrition Support

Nutrition support is critical in the management of trauma patients. The rationale is 3-fold: First, to prevent acute protein malnutrition; Second, to modulate the immune response; Last, to promote gastrointestinal structure and function [4].

4.1.1 Prevent Acute Protein Malnutrition

Patients would always develop a systemic inflammatory response syndrome (SIRS), which resolves with recovery, after the initial traumatic insult. However, in the condition of patients with overwhelming SIRS, hypercatabolism would result in acute protein malnutrition and subsequent immune system impairment. This persistent hypercatabolism dominates the metabolic response to trauma. If exogenous amino acids were not supplied timely, the initial demand would be met by skeletal muscle proteolysis. Thereafter, there is depletion of visceral structural elements, as well as circulating proteins. The resultant acute protein malnutrition is associated with subclinical multiple organ dysfunction (MODS).

4.1.2 Immune Response Modulation

SIRS, characterized by the localized and systemic production and release of multiple pro-inflammatory cytokines, is an acute condition following trauma. However, the traumatic insult also stimulates a parallel release of anti-inflammatory cytokines, called the compensatory anti-inflammatory response syndrome (CARS). Overwhelming CARS seems to be responsible for post-traumatic immunosuppression, leading to increased susceptibility to infections, sepsis and MODS. Compared to parenteral nutrition, the use of enteral nutrition has been shown to improve clinical outcomes, decreased infective complications and reduced the incidence of MOF in patients with SIRS and CARS. Previous studies to explain these effects suggest immunomodulatory effects of enteral nutrition on both the systemic and intestinal mucosal immune systems [5]. Our previous studies have also shown that early enteral nutrition could moderate the excessive immune response during the early stage in severe acute pancreatitis (SAP) patients [6]. The integrity of the intestinal epithelial and immune cells of the gut-associated lymphoid tissue and the intestinal barrier plays an important role in maintaining the intestinal homeostasis and preventing bacterial translocation. The intestinal epithelial cells (IEC)-derived cytokines secretion plays a major role both in maintaining intestinal mucosal functions and in the maturation and optimum functions of lymphocytes. While enteral nutrients play a major role in maintaining the integrity of IEC. As a result, enteral nutrition could modulate the intestinal mucosal immune systems.

4.1.3 Gastrointestinal Structure and Function Promotion

Gut dysfunction occurs in the majority of the critically ill patients. In trauma patients, gut dysfunction occurs for multiple reasons. First of all, trauma itself would cause an ischemia/reperfusion injury to the intestine. Subsequent therapies such as anesthesia and bowel manipulation would cause further injury to the intestine. Consequently, the dysfunctional gut becomes a reservoir for pathogens and leads to infection, sepsis as well as multiple organ failure (MOF). A series of

animal studies have demonstrated that enteral nutrition could promote the protective effects of commensal bacteria, maintain the mass of gut-associated lymphoid tissue and preserve gastrointestinal mucosal structure and function [7–9]. Furthermore, clinical studies have shown these effects translate into better outcomes with respect to infection, organ failure and length of hospital stay [10, 11].

4.2 Route and Time of Nutrition Support

Despite the widespread use of nutrition in trauma patients, there still remains controversial in the aspect of the route and timing of nutrition support.

4.2.1 Parenteral Versus Enteral Nutrition

Early in the 1970s, enteral nutrition was preferred over parenteral nutrition as it was less expensive, safer and more convenient. However, the gut was regarded as dysfunctional after the traumatic insult in trauma patients at that time. Therefore, the implementation of enteral nutrition was always delayed until the gut function was certain. By the late 1970s, there was a better understanding of resuscitation and stress metabolism, which provided the rational for early nutrition. By then, parenteral nutrition developed by Dr. Stanley J. Dudrick was widely used in the surgical patients [12]. Therefore, parenteral nutrition gradually became the standard way for nutrition therapy in patients with severe trauma.

While, in the 1980s, a series of studies documented the physiologic advantages of enteral nutrition over parenteral nutrition. The reasons were as follows: First, as enterally delivered substrates pass first through the liver, they would be better used. Second, enteral nutrition does not produce the glucose intolerance associated with parenteral nutrition. Last, it was reported that enteral nutrition could prevent intestinal mucosal atrophy and bacterial translocation as well as maintain immune function. Taken together, enteral nutrition had regained the popularity by the late 1980s.

Later then, several clinical studies have pointed out the harmful effects in the patients receiving parenteral nutrition. Moore et al. [13] compared the effect of total enteral nutrition and total parenteral nutrition in the patients with major abdominal trauma. Results showed that the incidences of infection and major septic morbidity were significantly higher in the patients of parenteral nutrition group compared to those of enteral nutrition group. Soon after, a study conducted by Kudsk et al. [8] confirmed these findings in 98 patients with blunt and penetrating abdominal trauma. They found that although patients with enteral nutrition received significantly fewer calories/kg, there was no significant difference in nitrogen balance between the two study groups. In addition, patients in enteral nutrition group suffered significantly fewer pneumonias (11.8 % vs. 31.0 %, $p < 0.02$), intra-abdominal abscess (1.9 % vs. 13.3 %, $p < 0.04$), and line sepsis (1.9 % vs.

13.3 %, $p < 0.04$) as well as sustained significantly fewer infections per patient ($p < 0.03$) compared to those in parenteral nutrition group.

In 2003, the Canadian Critical Care Clinical Practice Guidelines evaluated 12 level 2 studies and 1 level 1 study that compared enteral nutrition to parenteral nutrition in critically ill patients with an intact GI tract [14]. The results showed that although there was no apparent difference in mortality rates across groups receiving enteral nutrition or parenteral nutrition (relative risk [RR], 1.08, $p = 0.7$, the incidences of infectious complications were markedly reduced in the group of enteral nutrition compared with that of parenteral nutrition (RR: 0.61, $p = 0.003$). According to the results, the committee strongly recommended the use of enteral nutrition over parenteral nutrition for critically ill patients.

More recently, the updated Guideline for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient assessed six previous meta-analysis comparing EN with PN. The results revealed significant reductions in infectious morbidity with use of enteral nutrition. In conclusion, the committee also suggested the use of enteral nutrition over parenteral nutrition in critically ill patients including patients with trauma, burns, head injury and major surgery who require nutrition support therapy [15].

4.2.2 Early Versus Delayed Enteral Nutrition

As previously mentioned, a persistent hypercatabolic state dominates after trauma. This results in acute protein malnutrition and subsequent immune system impairment. If not timely supplied with exogenous nutrients, there would be a depletion of visceral and circulating proteins. Therefore, a series of clinical studies had been conducted to assess the implementation as well as the effect of early enteral nutrition in the trauma patients.

In 1986, Moore et al. first performed a prospective, randomized, controlled trial to evaluate the benefits of early enteral nutrition in 75 patients with major abdominal trauma [16]. Patients were randomly assigned to control group (no enteral nutrition within the first five postoperative days) or early enteral nutrition group (element enteral nutrition via a needle catheter jejunostomy initiated 18 h postoperatively). It turned out that the nitrogen balance was significantly improved ($P < 0.001$) and the infectious morbidity was significantly decreased ($p < 0.025$) in the early enteral nutrition group. According to these findings, the authors concluded that early enteral nutrition was feasible in the immediate postoperative period and that it decreased septic complications.

Later after that, Taylor et al. [10] performed a study to determine the effect of early enhanced enteral nutrition on clinical outcome in 82 patients suffering head injured. Patients were randomized to receive standard EN (gradually increased from 15 mL/h up to estimated energy and nitrogen requirements) or enhanced EN (started at a feeding rate that met estimated energy and nitrogen requirements) from day 1. The results showed that there was a tendency for more intervention patients to have a good neurologic outcome at 3 months than control patients (61 % vs.

39 %, $p = 0.08$). Fewer intervention patients had an infective complication (61 % vs. 85 %, $p = 0.02$) or more than one total complication (37 % vs. 61 %, $p = 0.046$) compared with control patients. These results indicated that early enhanced enteral nutrition appeared to accelerate neurologic recovery and reduced both the incidence of major complications and post-injury inflammatory responses. At the same time, Kompan et al. [17] conducted another study to determine the effect of early enteral nutrition on gut permeability and the development of MOF in multiply injured patients. They found that the patients started on enteral nutrition later than 24 h after admission to the ICU demonstrated increased intestinal permeability on the second day after sustaining multiple injury. In addition, those patients had a more severe form of MOF than the group with early enteral nutrition.

In 2003, the Canadian Critical Care Clinical Practice Guidelines Committee evaluated 8 randomized controlled trials (level-2 studies) comparing early with delayed enteral nutrition intake in critically ill patients with intact gastrointestinal tracts [14] and found that early enteral nutrition was associated with a trend toward a reduction in mortality (RR: 0.52, $p = 0.08$) when compared with delayed enteral nutrition. As a result, the committee recommended early enteral nutrition (within 24–48 h after admission to ICU) in critically ill patients. Later in 2011, Doig et al. [18] conducted a meta-analysis which included three randomized controlled trials (RCTs) with 126 participants and further confirmed the benefits of early enteral nutrition in the trauma condition. A more study by Chourdakis et al. [19] found a positive influence on endocrine function of early enteral nutrition. The results of their study showed lesser hormonal changes in the early enteral nutrition group compared with the delayed group, indicating that early enteral nutrition might exert beneficial effects on the hormonal profile of the patients with traumatic brain injury.

Lately, the updated Guideline for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient retrospected three meta-analyses aggregated data from RCTs comparing early versus delayed enteral nutrition in critically ill patients including trauma [15]. All the studies revealed a better outcome for the patients when early enteral nutrition was established. As a result, the committee recommended that, nutrition support therapy in the form of early enteral nutrition should be initiated within 24–48 h in the critically ill patient who is unable to maintain volitional intake.

Whereas, the role of early enteral nutrition for burns patients was still undefined yet. Patients with large burns have significantly increased energy requirements. Basal metabolic rates can double when burns are >50 % total body surface area (TBSA) [20]. These patients, as well as those with inhalation injury who require mechanical ventilation, are not able to meet their requirements for macro- and micronutrients and fluids via the oral route. Under these circumstances, enteral nutrition is indicated.

Providing nutrition is clearly essential in the successful management of burn injured patient, there are several conflicting findings amongst research groups regarding the optimal method and timing of enteral nutritional support. Providing early nutritional support has a number of advantages including increased caloric intake [21] and improving bowl mucosa integrity [22]. However, it has remained

unclear whether early enteral nutritional support has any beneficial impact on a diverse field of nutritional, metabolic and biochemical outcomes and clinical indicators such as length of stay, infection rates and mortality [23]. In 2007, Wasiak et al. performed a systemic review to examine evidence for the effectiveness and safety of early versus late enteral nutrition support in adults with burn injury and suggested that early enteral nutrition support might blunt the hypermetabolic response to thermal injury but was insufficient to provide clear guidelines for practice.

5 Conclusion

In summary, the metabolic response to trauma involves a number of changes in the metabolism of the major energy sources as well as protein metabolism and adequate nutrition support is pivotal in the management of trauma patients. During the procedure of nutrition support, enteral nutrition is superior to parenteral nutrition in critically ill trauma patients and early enteral nutrition was more preferred.

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