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Review article

NUTRITION IN PATIENTS WITH TRAUMATIC BRAIN INJURY
(NUTRITION IN PATIENTS WITH TBI)

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Summary

Traumatic brain injury (TBI) is a condition with a high morbidity and mortality rate. From a medical point of view, little can be done to prevent primary brain injuries. After the initial injury, a cascade of events at the cellular and molecular level, including cell swelling, changes in cell membrane permeability, influx of immune or inflammatory mediators, and release of excitatory neurotransmitters result in so-called "secondary" brain damage. Optimization in energy and protein provision has taken its place lately in the fundamental concept of treatment in critically ill patients with moderate and severe brain trauma, together with reducing intracranial pressure and prevention of hypotension and hypoxia.

Administration of medical nutrition adjusted to the phase of trauma in the right time of medical treatment, as well as choosing the most adequate method of nutrition with appropriate formulas, can decrease neuro inflammation, immunodeficiency and metabolic crisis. A particularly difficult and challenging task in patients with TBI are maintenance of glucoregulation and electrolyte balance, protein replacement, and fluid therapy. Therefore, medical nutrition plays a significant role in the recovery of neurotraumatized patients.

Key words: *enteral nutrition; parenteral nutrition; traumatic brain injury*

Introduction

Traumatic brain injury (TBI) is a structural brain injury that occurs as a result of an external force transmitted to the head with disrupting the normal architecture and structure of the brain[1,2]. This type of injury represents a significant socio-economic problem, resulting in high disability and mortality rate.[2] It is often associated with malnutrition, and these patients are in increased vulnerability of infection, they are prone to longer recovery and length of hospital stay. After an injury, a series of events follows, such as metabolic disorders, ischemia, hypoxia and reduced blood flow through the brain parenchyma, all of which cause the so-called "secondary brain injury" that can be prevented or at least alleviated. Among other strategies, adequate nutrition plays an important role.

Nutrition therapy, adequate glucoregulation and multimodal monitoring including the use of microdialysis catheter should be an integrated approach to patients with TBI in order to ensure adequate supply of oxygen, glucose and other nutrients to the nerve cells. The Glasgow Coma Scale (GCS), which has its own limitations such as subjectivity and the inability to assess the verbal response in intubated patients, remains one of the most frequently used scale for grading the severity of injuries[3].

The highest percentage of TBI, about 80% are mild with GCS 13-15, the 10% are moderate (GCS 9-12), and around 10% are severe (GCS 3-8).[3] Estimates of concurrent TBI in patients with primary traumatic SCI (spinal cord injury) range from 12.5 to 74.2% according to data from The National Spinal Cord Injury Statistical Center.[4] Initial imaging is determined by the protocol to properly assess the patient with dual diagnosis and it always should be assumed in all TBI when there is a disorder of mental status or blunt injury above the clavicle[5,6]. The estimated annual incidence of TBI is about 1.7 million, of which about 250.000 require hospital treatment.[1] They are common among children and adolescents, as well as among people over 65 years

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old. TBI is responsible for reducing the working capacity of 5-6.5 million people annually[1].

Mechanisms of injury

In general, according to the mechanism of injury, TBI can be divided into closed-head and penetrating. Closed-head injuries are caused by the blunt impact to the head. Penetrating injuries occur in conditions when a foreign body breaks the bones of the skull and penetrates the brain parenchyma (knife or bullet)[3]. In general, older patients have fewer physiological reserves, which makes the prognosis poor even for mild injuries[7].

Morbidity and mortality in neurosurgical injuries are closely related to increased intracranial pressure (ICP), the level of bleeding and contusions, as well as edema of the brain parenchyma[8,9]. After the initial, primary injury, the brain's energy needs increase, and this is achieved with oxidative metabolism of glucose. Inadequate supply of some of these substances leads to additional neurological damage and the occurrence of "second" brain injury. In addition to ischemia and hypoxia, these secondary damages also occur as a result of metabolic disorders, oxidative stress, immune dysfunction and increased permeability of blood-brain barrier[10]. Malignant brain edema has a particularly poor prognosis because it is often refractory to therapy and causes irreversible changes with a mortality rate of near 100% if untreated[11].

At the cellular level, biochemical changes begin within minutes of injury and progress over months[12]. After the acute phase, microglial cells remain active, and the process of neuro-inflammation continues which connects acute infection and chronic neurodegeneration, which are responsible for later cognitive disorders and development of dementia[13]. For these reasons, the prevention of secondary brain damage is crucial because it is something that can be prevented.

Hypermetabolism and hyper-catabolism after TBI occur as a consequence of the excessive secretion of endogenous hormones such as catecholamines and corticosteroids that antagonize the effect of insulin. This leads to hyperglycemia, loss of muscle mass, increased energy consumption, negative nitrogen balance and fluid and salt retention[14]. All of these are causes of immune disorders and an increased tendency of infection, sepsis and multi-organ dysfunction, which leads to prolonged ICU treatment, length of hospital stay and hospital costs[15]. The acute phase of hyper-catabolism can last several weeks, depending on the severity of trauma, then reaches maximum and a plateau after two months, which coincides with the beginning of the patient's rehabilitation[16].

One of the facts is that the energy expenditure increases by 87-200%[14]. The peak for resting energy expenditure is around 4-5 days after trauma and remains elevated for the next 9-12 days[17]. However, calculating energy requirement in acute phase is very challenging due to various factors such as an increase in body temperature, additional injuries, presence and the severity of infection, use of mechanical ventilation, sedative and relaxants. To calculate energy requirements, ASPEN (American Society for Parenteral and Enteral Nutrition) and ESPEN (European Society for Parenteral and Enteral Nutrition) recommend the use of indirect calorimetry, whenever possible[18,19]. If it is not available, other published predictive equation can be used as Harris-Benedict, Ireton-Jones, Mifflin-St Jeor, or a basic weight-based equation (25-30 kcal/kg)[17]. Also important, patients with TBI receive hyperosmolar solutions for reducing the ICP. This represents an additional challenge for clinicians to maintain adequate homeostasis of water and electrolytes, which requires frequent monitoring their levels in the blood[20].

Methodology

Data sources and searches

By reviewing the available data on PubMed, Scopus, Google Scholar and Cochrane Library the latest data related to nutrition in neurotraumatized patients were summarized. More than 20 papers were reviewed, and the most important recommendations are shown.

Nutrition therapy

a. Timing and route of feeding

In patients with moderate-to-severe TBI, optimizing nutrition by preventing malnutrition as well as using selected diet is a field that is still developing with the aim of mitigating secondary brain injury and promoting cellular recovery. For

now, there is little scientific evidence and recommendations in this area due to rigorous clinical trials and conflict data from the literature.

Malnutrition often goes unrecognized in hospitalized patients, and it is thought that one third of patients develop this disorder at some point during hospitalization[21]. It is believed that the prevalence of malnutrition is around 78%[10] and such a high prevalence is explained by catabolism induced by inflammatory cytokines during the critical phase of illness, where there is a mobilization of amino acids from skeletal muscles and negative nitrogen balance. Malnutrition is more often present in severe trauma patients with lower GCS values. Immobilization, dysphagia and insufficient caloric intake additionally contribute to malnutrition.[22]

b. Early vs. late nutrition

Although the definitions in literature vary, early enteral nutrition (EN) is defined as one that is started in the first 24-48 h, while late is started after 48 h.[18,19] The benefit of early enteral nutrition consists in preserving the integrity of gastrointestinal mucosa, preventing the bacterial translocation and endotoxemia in systemic bloodstream, preventing malnutrition and promoting neurological recovery, but due to inconsistency of data, significant debate existed over aggressive early nutrition and how quickly to increased calorie. The EPaNIC study[23] showed that early parenteral nutrition can have a negative impact on patient's survival. In acute early phase of critical illness, at a time when the nutrition substrates cannot be utilized, should avoid overfeeding, preserve (adaptive) mitochondrial function (hibernation, autophagy).[24]

Nevertheless, in severe TBI, numerous studies have proven the benefit of early EN in muscle mass preservation, promoting cerebral homeostasis, improving endocrinologists factors, reducing inflammatory responses.[25,26] If the level of consciousness or using the mechanical ventilation does not allow oral diets, early nutrition within 24-48 h and even 72 h is recommended according to ASPEN and ESPEN[18,19]. Brain Trauma Foundation study[27] showed that early EN and every 10 kcal/kg/day increase in energy intake reduces mortality by 30-40%. Even though the evidence clearly points out the benefits of early EN, due to inconsistency of evidence, it is recommended that the basal energy needs can be reached by the fifth day, and at the latest by the seventh day after TBI.[28] Some of the reasons for concern regarding early EN are related to the risk of aspiration pneumonia, gastrointestinal dysmotility and increased metabolic demand.

c. Enteral vs. parenteral nutrition

Patients suffering from serious brain injury, together with other patients unable to take food by mouth, should meet their energy demands by special enteral nutritive formulas through nasogastric or jejunal tubes, or parenteral nutritive solutions. Enteral formulas are mainly standardized as polymers, oligomers, and monomers. Patients treated with medical nutrition enriched with proteins and amino acids showed better wound healing, tissue recovery and biosynthesis of biologically active peptides than fasted patients.[29]

Decrease or discontinuation of enteral stimulation leads to increase of proinflammatory cytokines in enterocytes, resulting in apoptosis, epithelial barrier disfunction and disturbance in enteral microbiome. Anatomical and functional changes in enteral epithelia increase the risk of nosocomial infections, prolonged hospital treatment, and mortality[18,19]. Parenteral nutrition (PN) avoids digestive system, has no protective effect on enterocytes, and increases the risk of infections.

However, EN should not be administered to patients with hemodynamic instability, uncontrolled, life-threating hypoxemia, hypercapnia, acidosis, active gastrointestinal bleeding, and bowel ischemia or bowel obstruction[1,19]. The mechanism implies increased mesenterial blood flow following EN, which leads to increased oxygen demands. In hemodynamically unstable patients this can lead to bowel ischemia, necrosis or perforation.[30,31] On the other hand, in hemodynamically stabile patients both ASPEN and ESPEN favorize EN comparing to PN.[18,19]

Current knowledge about medical nutrition undoubtably supports EN vs. PN mainly because of its protective effect on gastrointestinal mucosa, immune support, decreased risk of infections, and shorter stay in ICU.

One of the leading problems with EN is a frequent occurrence of gastrointestinal intolerance mostly manifested in diarrhea or decreased bowel motility, which often results in inconstant feeding and malnutrition. Studies showed that over 30% of

the patients with TBI do not receive targeted calorie intake, even when monitored by experienced and motivated intensivists. The estimation is that approximately 50% of the patients with TBI manifest some kind of gastrointestinal intolerance[32]. There are several identified factors in the background, and the most common are: prolonged gastric emptying caused by increased intracranial pressure, impaired function of autonomic nervous system, and use of certain medications, such as opioids and phenobarbital[32]. Prolonged gastric emptying may increase residual gastric volume, which may cause aspirational pneumonia. Gastrointestinal hypokinesia usually persists for 1-2 weeks after TBI onset.[33] Paralytic ileus is a frequent complication of traumatized patients in general, especially with SCI and during prolonged immobilization. Early EN reduces the development of ileus.[34]

There are several strategies to improve EN tolerance: elevation of the headboard for 30—45^0 C, transgastric jejunal feeding, continuous versus bolus feeding[29,35], use of concentrated formulas (>1.5 kcal/ml)[34], and administration of the drugs which stimulate gastrointestinal motility, as metoclopramide and erythromycin. ESPEN suggests that post-pyloric feeding should be used in patients resistant to prokinetic therapy[18]. The common opinion is that jejunal feeding should start only if technical conditions are fulfilled.

There are no certain recommendations when to start EN in patients receiving vasopressors, but the literature considers that safe doses are lower than 70.14 μ/kg/min noradrenaline, 3-10 μ/kg/min dopamine, and 12 μ/kg/min dobutamine[36].

A diet providing 10-20 kcal/hour is defined as trophic EN, and it may be sufficient to prevent enterocyte atrophy, as well as to maintain digestive system integrity. Some authors concluded that this type of diet (<600 kcal/day) within 48 h from TBI onset reduces the total number of days under mechanical ventilation and shortens the length of medical treatment without increasing the risk of complications compared to the patients who did not receive EN[18,37]. They highlight the beneficial effect of early trophic EN in patients with TBI.

It is important to note that the decision whether to start EN or not should be made individually for each patient, based on clinical presentation, hemodynamic stability, and the presence of contraindications or potential risks.

Parenteral nutrition (PN) is nutrition based on special solutions administrated through intravenous lines in patients who have contraindications for EN. Otherwise, EN has the advantage over PN, considering that PN is associated with a higher risk of infections and prolonged medical treatment. A study comparing early PN (<48 h) with late PN (after day 8) showed faster recovery, fewer infectious complications and less consumption of hospital resources in the late PN group[38].PN should be considered within days 3-5 of hospital treatment in patients that have contraindications for EN[19].The cause of the harmfulness of ultra-early PN is not fully understood, but it is familiar that excessive PN feeding increases the risk of bacterial infections[39]. PN is also associated with hepatotoxicity and cholestasis, which are thought to result from impaired enterohepatic circulation[40]. Clinical practice showed that patients receiving PN require more frequent monitoring of electrolytes and cardiac function.

So far, there are no defined guidelines on when to start supplemental PN. ESPEN recommends it should be between days 4 and 7 of hospital treatment, while ASPEN considers it should be between days 7 and 10, but only if it is not possible to achieve over 60% of the energy needs by EN[18,19].

Cerebral microdialysis is an invasive technique in which microcatheter is placed deep into the brain tissue. The microcatheter is a semi-permeable membrane that allows the measurement of metabolite concentrations in the extracellular fluid. Monitoring the levels of glucose, pyruvate, lactate, and glutamate, together with the measurement of intracranial pressure, cerebral oxygenation and EEG, may indicate certain clinical interventions that would prevent secondary brain damage. An increased lactate/pyruvate ratio coupled with decreased extracellular glucose levels may predict ischemic strokes, epileptic seizures and intracranial hypertension[41]. This type of monitoring is widely used in early detection of ischemia and metabolic crises in the brain.

Glucose metabolism

The brain plays an important role in glucose metabolism[41]. Therefore, strokes, TBI and other neurological injuries may cause impaired glucose metabolism. Metabolic stress and hyper-catabolism

caused by surgery or glucocorticoids, catecholamines and glucagon excess result in an increase of resting energy expenditure up to 200%. This metabolic disorder leads to glycogenolysis and gluconeogenesis, often coupled with hyperglycemia, resulting in excessive protein consumption, particularly in muscles[24,42]. Despite the vital importance of glucose for ATP production, pronounced hyperglycemia may be harmful in several ways. Glucose can directly cause peroxidation of cellular membranes[43]. Insulin resistance and prolonged hyperglycemia disrupt astrocyte metabolism and inhibit their proliferation[44]. This implies that maintaining blood glucose levels within certain limits improves the outcome in patients with TBI[45]. On the other hand, aggressive insulin therapy aiming to lower blood glucose levels may result in energy crisis (monitored by lactate/pyruvate ratio and glutamate levels) and hypoglycemia in brain tissue[46]. The NICE-SUGAR study showed that patients with blood glucose levels of 4.5-6 mmol/L have more frequent hypoglycemic episodes than those with tolerated levels of <10 mmol/L[47].

The lactate/pyruvate ratio reflects brain metabolism, and its increase may indicate mitochondrial dysfunction[48] or reduced oxygen supply due to ischemia or hypoxia[49].

A decreased concertation of glucose in the brain may result from various pathophysiological mechanisms. Glucose levels lower than 0.7 mmol/L measured by microcatheters in ischemic stroke lead to impaired brain metabolism[50]. A glucose concentration <1 mmol/L is an independent risk factor for reduced cerebral blood flow (<35 ml/100g/min).[51]

As the most important energy substrate for brain tissue, glucose supply has to remain in optimal range in order to preserve brain functions. Achieving this goal requires an understanding of the overall interaction between nutritional therapy, insulin therapy, and brain metabolism, which can be measured by bedside microcatheters, if necessary.

Current evidence indicates that lactates, ketone bodies, and branched-chain amino acids (BCAAs) may be preferred energy substrates during metabolic crises, in order to reduce the potentially harmful effects of insulin.

Considering all previous recommendations and evidence, the Brain Trauma Foundation suggests implementation of early EN, within 24 hours, with at least 50% of total energy needs met, with aggressive progression to full calorie intake, depending on the presence of reduced glucose levels in the brain tissue and increase in the lactate/pyruvate ratio. So far, permissive hyperglycemia with blood glucose levels of 8-11 mmol/L is recommended by guidelines.[52]

Protein supplementation

The importance of protein far exceeds that of protein as a source of calories. They are the most important caloric nutrient for the recovery of a damaged brain, for maintaining adequate immune function and maintaining body weight. Most critically ill brain-injured patients have a high ratio of protein needs to total energy needs, and these needs are difficult to meet with standard EN. Nitrogen excretion increases independently of replacement and a stable level of nitrogen loss can last up to 4 weeks after trauma[15].

ASPEN-SCCIM recommendations suggest starting EN with high-protein polymer formulas within 24-48 h after trauma in hemodynamically stable patients[17]. Energy needs in the acute phase are 25-30 kcal/kg/day, and protein needs can vary from 1.2-2 g/kg/day, and the share of protein in the total caloric intake should be 15-20%[51].

Clinicians must know the amount and concentration of protein they give to patients with head injury through enteral nutrition, because the intake of large amounts of protein and insufficient water, with moderate salt intake can be the reason for "tube feeding syndrome" characterized by hypernatremia, azotemia and dehydration[53,54].

The ketone body diet

Although it has long been known that such diets are beneficial for children with resistant or rare metabolic causes of epilepsy, recent literature also recommends them for head trauma. This diet is high in fat, moderate in protein and very low in sugar. The theoretical mechanism of benefit includes providing alternative energy levels through ketone bodies, benefiting the maintenance of the gut microbiome, increasing lipid repair and stability of the cell membrane, antioxidant effect and prevention of mitochondrial dysfunction. The benefit

is attributed to the ability of ketone bodies to be resistant to oxidative stress and to maintain mitochondrial stability[55,56].

Astrocytes play a major role in the regulation of oxidative metabolism in the brain and can benefit from exogenously introduced ketone bodies. Given their perivascular localization, they are the main site of glucose uptake and metabolism. They produce lactates that participate in the transfer of oxidative metabolism in the brain[57]. In addition to lactate, astrocytes produce an additional amount of ketone bodies. From this, it is concluded that astrocytes can participate in the transfer of lactate and ketone bodies as a substrate in the oxidative metabolism of the brain and the maintenance of homeostasis in cases of excessive synaptic activity and ischemia that accompany acute brain damage[58]. Administration of hypertonic lactate solution reduces ICP, glutamate level, increases glucose level in brain and increases blood flow through brain tissue[16]. It is even thought that this solution can replace mannitol and hypertonic saline (3% NaCl) in patients with TBI and increased ICP.

As there is not a sufficient number of studies and evidence for everything, this type of therapy remains in the domain of future research[59].

In addition, high concentrations of ketone bodies reduce glutamate concentrations in the synaptic cleft, resulting in decreased neuronal excitability[60,61]. Observational studies have shown, using a microdialysis catheter, that the concentration of ketone bodies is the highest immediately after the injury, and therefore ultra-early nutrition in this period may have a harmful effect on these patients.[62]

Considering all the above, there are studies where succinate supplementation is mentioned. Local administration of succinate (preferably through a microdialysis catheter) reacts directly with the mitochondrial electron transport chain, improving brain metabolism and mitochondrial function itself. [63]

Omega-3 fatty acids

Their use in the ICU is increasing, but their role in patients with head injuries is still unclear. Eicosanoid precursor fatty acids include omega-3 polyunsaturated fatty acids such as eicosatetraenoic acid (EPA) and docosahexaenoic acid (DHA). Their metabolites have anti-inflammatory activity, which is exactly the opposite of the effect of omega-6 fatty acids. At the site of injury or damage, these metabolites participate in killing and cleaning pathogens, reduce leukocyte infiltration and stimulate macrophages[64]. In addition, they inhibit the production of proinflammatory cytokines and chemokines. These metabolites reduce neuroinflammation and neuronal death in epilepsy[65], Alzheimer's disease[66], SAH ischemic stroke[67].

A study by Hasadri et al. demonstrated that omega-3 fatty acids reduce mitochondrial dysfunction, cell apoptosis, glutamate-induced excitotoxicity, and inflammation caused by oxidative stress[68]. In the beginning, the diet contained almost the same ratio of omega-6 to omega-3 fatty acids, but recently this ratio has changed from 2:1 to 8:1 in favor of omega-3 fatty acids, and where the proportion of fat 25-40%, i.e. 2-6 g/day of omega-3 fatty acids[69].

So far, there is not a large number of randomized controlled studies that have examined the use of omega-3 and omega-6 fatty acids in the reduction of secondary brain damage. Despite these limitations and knowing the good properties and already known mechanisms of action of omega-3 FA, it is certain that in the future it will find a place in the treatment of neurotraumatized patients.

Other types of immunonutrition

Other immunonutrients include glutamine, arginine and ribonucleic acids, which are used in combination with omega-3 FA. It is believed that when given, they have a synergistic effect that is greater than when given separately, especially among oncological and surgical patients[70,71,72]. The role of immunonutrients is based on their anti-inflammatory effect and the provision of essential nutrients such as glutamine and arginine, whose reserves are quickly consumed during catabolism. Glutamine plays a role in cell proliferation, as an element of ATP synthesis and glycogenesis, maintenance of acid-base status and as an immunomodulator[70]. Arginine serves as a substrate for the synthesis of several cellular proteins such as nitric oxide, polyamines, glutamic acid, ornithine, proline and creatine. Nucleotides and their metabolite additionally stimulate the proliferation of lymphocytes and enhance the function of natural killer cells and macrophages[73].

Although it is known that immunonutrition has a place in the treatment of cancer and traumatized patients, the precise role of individual immunonutrients in specific diseases such as stroke and head injuries are still in the research stages. The 2016 SCCIM AND ASPEN recommendations suggest immunonutrition in patients with TBI[18,74].

Zinc and magnesium

Although it is known that zinc deficiency can be harmful, its supplementation is still more controversial than TBI. Magnesium is thought to have more than a protective role in preventing excitotoxicity and maintaining normal cell function after neurological injury[75,76], but its supramaximal supplementation is not part of daily practice.

Recent research highlights the role of adequate maintenance of gut microbiome homeostasis in neurological injuries by supporting the modulation of immune, inflammatory and metabolic processes via the microbiota-GIT-brain axis[77].

Conclusion

Nutritional therapy is part of an integrated approach to the treatment of neurotraumatized patients. This approach includes early and optimized nutrition, control of glycemia and electrolytes, as well as multimodal monitoring using microdialysis catheters in order to better optimize neuron metabolism and prevent neuron distress. This is the best way to prevent secondary brain damage and improve the outcome in the treatment of neurotraumatized patients.

Early enteral feeding is novel useful in such infants and is recommended by various associations. However, one should keep in mind slow gastric emptying as one of the consequences of increased ICP and implement strategies to improve it. If enteral nutrition is contraindicated, progressive parenteral nutrition within 3-7 days is recommended. Maintenance of the so-called "permissive glycemia" with values of 8-11 mmol/L and protein compensation (15-20% of total energy needs, up to 2 g/kg body weight) are also some of the ESPEN and ASPEN recommendations. Although it is known that immunonutrition has a place in the treatment of traumatized patients, the precise role of individual immunonutrients in specific diseases such as stroke and head injuries as well as the use of ketogenic diets are still in various stages of research.

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