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Review Article

The Role of Nutrition on Brain Injuries

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Abstract

Road traffic accidents are the most common cause of Traumatic Brain Injury (TBI). Patients who suffer from brain injuries can exhibit a wide range of symptoms depending on the nature and type of injury. The severity of TBI is generally classified as mild, moderate, or severe based on the Glasgow Coma Scale (GCS), which objectively measures the level of impaired consciousness. A GCS score of 8 or below indicates severe TBI and necessitates admission to intensive care and the use of mechanical ventilation. These patients experience significant metabolic changes due to the excessive production of endogenous catabolic hormones following the injury. The nutritional requirements of these patients vary depending on the severity of the trauma and the phase of the illness. Initiating timely feeding and addressing individualized nutritional needs can help prevent malnutrition. Additionally, nutrition plays a crucial role in neuronal recovery and directly impacts neuronal plasticity, thus influencing the prognosis. Early involvement of nutritional support as part of comprehensive care is essential for recovery and improved outcomes. The purpose of this review is to provide an overview of the current evidence-based nutrition therapy for patients with TBI in critical care settings. The review will cover energy and nutrient requirements, enteral and parenteral nutrition, as well as the challenges associated with it.

Keywords: Brain; Nutrition; Brain injury; TBI

Introduction

Traumatic Brain Injury (TBI) is often labeled as a "silent epidemic" due to its global annual estimate of 69.0 million cases. TBI resulting from road traffic collisions is particularly concerning as it is the leading cause of disability and mortality [1,2]. The worldwide incidence of TBI from all causes in 2019 was calculated to be 939 cases per 100,000 individuals. Data on severe TBI is limited and varies by country and region, affecting around 73 cases per 100,000 people annually globally. These numbers are notably higher in low- and middle-income countries. The financial burden of medical treatment and rehabilitation for TBI patients is substantial and poses challenges to healthcare systems. Mortality rates are closely linked to the severity of TBI, with severe cases having a mortality rate as high as 49.7%. The risk of mortality is 2.47 and 7.19 times higher in severe TBI cases compared to moderate and mild cases, respectively [1,3].

The management of TBI patients focuses on preventing secondary brain injury that can occur as a consequence of the initial insult. This approach, known as cerebral resuscitation, involves maintaining adequate cerebral perfusion pressure, preventing hypoxia, and ensuring normothermia, normoglycemia, and normocarbia [4]. The primary injury results from direct mechanical trauma, leading to tissue damage, axonal shearing, and disruption of the Blood-Brain Barrier (BBB). On the other hand, secondary injury begins shortly after the primary insult and involves a series of molecular and biochemical changes. These changes include the release of inflammatory cytokines, excitatory neurotransmitters (such as glutamate and aspartate), mitochondrial dysfunction, and the generation of reactive oxygen and nitrogen species, ultimately causing excitotoxicity and cerebral edema [4,5].

This modification will result in an increase in the secretion of naturally occurring hormones, specifically corticosteroids, catecholamines, and glucagon, along with proinflammatory cytokines such as tumor necrosis factor-α, interleukin-1, and interleukin-6. This increase leads to states of hypermetabolism and hypercatabolism [6]. Consequently, there is an increase in both systemic and cerebral energy requirements, which leads to the consumption of lean body mass and a negative nitrogen balance. These effects have a significant impact on recovery and mortality rates.

At the molecular level, the release of the excitatory neurotransmitter glutamate following trauma causes an influx of calcium ions into neuronal cells, resulting in calcium dysregula-

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tion. This dysregulation interferes with both the electron transport chain and oxidative phosphorylation, thereby affecting cellular metabolism and energy production [5]. The imbalance of energy formation in injured brain tissues contributes to the formation of Reactive Oxygen Species (ROS) and free radicals [5]. Diets high in sugar or fat can further exacerbate oxidative stress by increasing the formation of free radicals [7]. The brain, with its abundance of circulating unsaturated fatty acids and oxygen, is particularly susceptible to oxidative stress following lipid peroxidation [7]. ROS play a role in triggering and activating proinflammatory factors such as interferon-γ, tumor necrosis factor TNF-α, and inducible nitric oxide synthase (iNOS) [8,9]. Nitric Oxide (NO) homeostasis is significantly affected in traumatic brain injury [5]. The upregulation of neuronal and endothelial Nitric Oxide Synthases (NOS) after TBI plays a crucial role as a vasodilator in maintaining cerebral blood flow [5,10]. However, intracellularly produced NO by iNOS leads to the accumulation of reactive nitrogen species [5,8,9,11]. The presence of these free radicals causes oxidative damage at the molecular level, ultimately resulting in neuronal death [8,9].

In addition, individuals with Traumatic Brain Injuries (TBI) may experience various other associated injuries. Pain and discomfort resulting from craniofacial trauma and prolonged cervical immobilization with a cervical collar can hinder the timely initiation of enteral feeding [12]. TBI patients face a heightened risk of malnutrition due to interruptions in feeding caused by the necessity for surgical interventions or procedures, as well as other patient-related factors [13]. Moreover, alterations in eating patterns, such as decreased appetite, can be attributed to psychological issues, particularly post-traumatic depression [14]. Patients with severe TBI often require intubation for an extended period, and upon extubation, they may encounter difficulties with swallowing, even when consuming modified diets, due to pharyngitis or facial injuries, as well as reduced appetite linked to hormonal changes associated with trauma. Attaining the recommended caloric intake in TBI patients may prove challenging due to the various mechanisms previously discussed that can directly or indirectly impact brain recovery. The production of essential proteins like Brain-Derived Neurotrophic Factor (BDNF) plays a critical role in neurogenesis, synaptogenesis, and cognitive function. Maintaining a balanced nutritional regimen is vital in regulating the levels of these proteins, as a diet high in fat and sucrose can diminish BDNF levels and negatively impact neuronal plasticity. Therefore, providing optimal nutrition support to critically ill patients is essential for enhancing both short- and long-term recovery [4].

Methods and Materials

The following databases were searched for this review article: To find the most significant comparative research on the relationship between Nutrition and Brain injury, its therapeutic options, the role of Nutrition on the treatment of Brain injury, and the effects of accidents on brain, search engines like Google Scholar, PubMed, and Directory Open Access Journal databases. Keywords like brain, nutrtion, injuries, diets, low carbohydrate, high fats, brain injuries, over weight, metabolism, medical nutrition, feeding strategies,and immune enhancing nutrition are also used. After assessing the quality and strength of the findings, meta-analyses, systematic reviews, large epidemiological studies, and randomized control trials were used as the main sources of information where they were available.

Results

Initiation of Nutrition

According to the terminology recommendations of the European Society for Clinical Nutrition and Metabolism (ESPEN), Medical Nutrition Therapy (MNT) encompasses oral nutritional, Enteral Nutrition (EN), and Parenteral Nutrition (PN) [16]. The initiation of early medical nutrition therapy is crucial in counteracting the acute catabolic state and has been shown to improve outcomes and reduce mortality rates [4,17]. Recent systematic reviews and various studies have confirmed the benefits of early feeding in Traumatic Brain Injury (TBI) patients, including the preservation of muscle mass, promotion of cerebral homeostasis, improvement of endocrinologic factors, reduction of inflammatory responses, and enhancement of the Glasgow Outcome Scale (GOS) at 3 months [4,18].

Both the American Society for Parenteral and Enteral Nutrition-Society of Critical Care Medicine (ASPEN-SCCM) and ESPEN guidelines recommend early enteral nutrition (within 24-48 hours) for critically ill adult patients [16,19]. The achievement of early enteral feeding has been found to be protective and associated with a lower risk of infectious complications, such as early-onset Ventilator-Associated Pneumonia (VAP), central nervous system infection, urinary tract infection, bacteremia, and a subsequent reduction in the length of ICU stay [4,18,20,21].

Furthermore, early enteral feeding has emerged as an independent factor influencing mortality rates. Feeding within the first five days after injury is significantly correlated with a decline in 2-week mortality. If patients are not fed within 5 and 7 days, there is a 2- and 4-fold increase in mortality, respectively [17,20–22].

Feeding Techniques

Nutrition support for patients with Traumatic Brain Injury (TBI) can be achieved through two routes: enteral (gastric, jejunal) or parenteral. Enteral nutrition, which involves feeding through the gastrointestinal tract, is widely accepted as the preferred method due to its associated benefits. A study conducted by Chiang et al. analyzed data from TBI patients with a Glasgow Coma Scale (GCS) score of 4-8 from 18 hospitals in Taiwan between 2002 and 2010 [23]. The results showed that patients who received enteral nutrition had a higher survival rate, a better GCS score on Day 7 of Intensive Care Unit (ICU) admission, and improved outcomes at 1 month post-injury [6,24,25]. Three review articles on TBI patients also supported enteral nutrition as the preferred approach to nutrition therapy, citing reduced risks of hyperglycemia, infection, cost-effectiveness, and fewer complications related to catheter use [26]. The updated guidelines from the Brain Trauma Foundation (BTF) for the management of severe TBI recommended early transgastric jejunal feeding to reduce the incidence of Ventilator-Associated Pneumonia (VAP) by reducing gastric residual volume. Enteral nutrition not only enhances mucosal blood flow but can also be administered at lower rates to prevent overfeeding while supporting the gut mass and barrier function [18,25]. It stimulates gastrointestinal postprandial hyperemia, which counterbalances the alterations in GI blood flow caused by increased intrathoracic pressure during vasopressor use, leading to an increase in Gut-Associated Lymphoid Tissue (GALT) expression. Furthermore, enteral nutrition provides a better delivery of macronutrients such as medium-chain triglycerides and fiber, resulting in the production of short-chain fatty acids, as well as essential

micronutrients like vitamins and minerals. The European Society for Clinical Nutrition and Metabolism (ESPEN) recommends the use of continuous enteral nutrition rather than bolus feeding [12,13,18,25,27]. A retrospective cohort study conducted in a neurosurgical ICU found that continuous feeding was better tolerated than bolus feeding among patients with acute brain injuries [16,28].

Conversely, PN is linked to disturbances in fluid and electrolytes, hepatic steatosis, higher occurrence of bacteraemia, mucosal sloughing, and malnutrition due to inadequate villous stimulation [12,25]. Parenteral nutrition serves as an alternative method for patients who cannot start early enteral nutrition. For traumatic brain injury patients with abdominal injuries, early parenteral nutrition is recommended to meet caloric needs and maintain positive nitrogen balance during the acute phase [25]. For patients requiring long-term enteral nutrition, a more secure access like Percutaneous Endoscopic Gastrostomy (PEG) is preferred over nasogastric access due to reduced risks of patient discomfort, tube displacement, and sinusitis. The placement of a PEG tube is advisable when the patient's overall condition is stable without active infection or acute intracranial events [12].

After sustaining a brain injury, the patient will experience a state of hypermetabolism and hypercatabolism. This metabolic crisis can have detrimental effects on other parts of the body. In brain injured patients, the hypermetabolic state leads to a significant increase in energy expenditure, ranging from 40-200%, when compared to individuals of similar gender, age, height, weight, and activity level. The highest levels of energy expenditure are observed in patients exhibiting decerebrate or decorticate activity [29,30].

On the other hand, hypercatabolism is a condition that occurs following trauma, surgery, or sepsis, and it triggers excessive breakdown of muscle and adipose tissue, resulting in weight loss and wasting. During the initial acute phase, glycogen stores are rapidly depleted, necessitating the utilization of muscle proteins as an energy source. This leads to a significant loss of lean body mass and a negative nitrogen balance. Additionally, electrolyte imbalances, increased susceptibility to infection, prolonged hospital stays, and higher mortality rates are common complications associated with hypercatabolism [4,31-33].

In non-stressed individuals, the average daily muscle loss is approximately 200-300 grams, whereas patients with traumatic brain injuries can lose up to 1000 grams of muscle per day. The release of chemical mediators such as cortisol, glucagon, catecholamines, and cytokines following trauma contributes to this heightened catabolic state, resulting in the breakdown of muscle tissue rather than fat for energy production [34].

The European Society for Clinical Nutrition and Metabolism (ESPEN) recommends the use of Indirect Calorimetry (IC) to determine Energy Expenditure (EE) in critically ill patients who are mechanically ventilated [6,16]. IC is also utilized to measure Resting Energy Expenditure (REE) and plays a crucial role in delivering and monitoring nutritional support. Accurately assessing the caloric requirements of patients is essential in providing adequate nutrition and promoting recovery [12].

Ideal Calorie and Protein Intake

Maxwell and colleagues proposed that patients with severe Traumatic Brain Injury (TBI) who do not receive Indirect Calorimetry (IC) and instead undergo enteral nutrition based on the Resting Energy Expenditure (REE) estimated using the Harris-Benedict Equation (HBE) may face the risk of being underfed, resulting in a negative nitrogen balance by the seventh day [35]. TBI patients demonstrate a wide range of increased baseline energy expenditure when using the HBE [12]. The use of sedation, paralytic agents, and barbiturates can impact the accuracy of estimation with this equation [12]. ASPEN-SCCM and numerous healthcare providers suggest that IC serves as the current "gold standard" for determining energy needs in TBI patients. In cases where IC is not feasible, a published predictive equation or a basic weight-based equation (25-30 kcal/kg/day) can be utilized to estimate energy requirements [6,33]. It may be acceptable to provide 50-80% of estimated energy needs for acute TBI patients in the ICU within the first 24 to 72 hours. A higher percentage of energy intake during the acute phase could be harmful, particularly in TBI patients where blood sugar management is crucial. Beyond 72 hours, the goal should be to meet full energy requirements. Consideration may be given to higher protein intake ranging from 1.5 to 2 g/kg/day in this patient population, as significant protein losses (20-30 g/L) are observed. While most TBI patients are not malnourished upon admission, they may develop malnutrition during their ICU stay, especially if they have other injuries [16]. These at-risk patients may not be identified by the NUTRIC score, as there is a notable loss of muscle mass that correlates with the duration of hospitalization and functional level at three months. Many of these patients are underfed, receiving only 58% of their energy needs and 53% of their protein requirements. Following discharge, the nutritional deficiency persists [36]. Both hyperglycemia and hypoglycemia can manifest in TBI patients, with hyperglycemia being more prevalent due to increased insulin resistance and elevated levels of stress hormones. Hyperglycemia is linked to unfavorable outcomes in these patients [4,12,25].

Multiple studies conducted on general ICU patients have shown that maintaining good glycemic control through the use of exogenous insulin leads to significant improvements in outcomes for critically ill individuals. However, it is important to note that the implementation of intensive insulin therapy with tight glycemic control may have negative effects on patients, particularly those with severe Traumatic Brain Injury (TBI) [37,38]. This is primarily due to the constant delivery and level of insulin associated with intensive insulin therapy, which can increase the risk of hypoglycemia in enterally fed patients. These patients are more susceptible to variations in the rate of food absorption from the gastrointestinal system and interruptions in their normal feeding [32].

Determining the optimal blood glucose level for patients with TBI remains a topic of debate, and recommended levels may vary depending on the severity and stage of the injury [39,40]. In general, maintaining glucose levels between 6 and 10 mmol/L would be a reasonable approach, similar to that recommended for other critically ill patients.

Nutrition to Boost the Immune System

Immunonutrition, a form of immune-enhancing nutrition therapy, involves modifying standard nutrition by incorporating specific nutrients like arginine, glutamine, omega-3 fatty acids, nucleotides, and antioxidants such as copper, selenium, zinc, and vitamins B, C, and E. Studies have shown that immunonutrition can enhance host immunity, regulate inflammatory responses, reduce infection rates, and shorten hospital stays [6]. In cases of Ttraumatic Brain Injury (TBI), where neuroinflamma-

tion, free radical production, and oxidative stress occur, immunonutrition therapy has been found to lower cytokine and IL-6 serum levels while increasing glutathione levels [33,41,42]. This indicates improved antioxidant defense, reduced inflammation, modulation of Systemic Inflammatory Response Syndrome (SIRS), and enhanced immune response [23,34]. Patients receiving immunonutrition therapy also tend to have higher prealbumin levels, indicating better nutritional status during hospitalization. However, the optimal composition of immunonutrition therapy remains uncertain and may vary depending on the severity of the injury and any existing comorbidities [19]. Well-designed multicenter Randomized Controlled Trials (RCTs) are necessary to determine the ideal composition, timing, duration, and clinical benefits of this type of nutrition for TBI patients.

Monitoring the adequacy of nutrition and identifying feeding-related complications are crucial components of optimal medical nutrition therapy. This is essential to ensure that the body receives an adequate amount of calories and nutrients to maintain body mass composition, support brain metabolism, and facilitate recovery. The use of indirect calorimetry is recommended to determine the specific energy requirements of each individual. The risk of malnutrition significantly increases after 48 hours of being in the intensive care unit. Clinicians should regularly conduct a comprehensive clinical assessment to detect any signs of malnutrition in these patients [16,6].

In addition to the risks of over or underfeeding, patients with traumatic brain injuries are also susceptible to developing feeding intolerance, hyperglycemia, hypoglycemia, electrolyte imbalances, and ileus. Feeding intolerance is a broad term used to describe conditions such as high gastric residual volume, abdominal distension, vomiting, diarrhea, or reduced bowel movements. These clinical issues are common among traumatic brain injury patients due to factors such as being comatose, requiring ventilatory support, experiencing elevated intracranial pressure, and often being prescribed sedatives and narcotics [12,13,18]. For patients experiencing diarrhea, the use of prokinetic agents should be avoided, and the addition of soluble fiber supplements to standard feeds or the use of small peptide semi-elemental formulas should be considered. In cases of abdominal distension, gastric paresis, or high gastric residual volume that is not resolved with prokinetic agents, post-pyloric feeding is recommended. Enteral naloxone and intravenous neostigmine have been found to be effective in treating paralytic ileus, particularly if it is opioid-induced [6,16]. Electrolytes such as potassium, magnesium, and phosphate should be monitored at least once daily during the first week of treatment. For patients at risk of refeeding syndrome, electrolyte levels should be checked 2-3 times a day and supplemented as necessary [16].

Discussion

Despite widespread recommendations for early enteral feeding, significant gaps persist in actual implementation, resulting in suboptimal nutrition therapy. Clinicians encounter challenges in initiating early feeding in trauma patients due to hemodynamic instability following initial blood loss, uncertainty regarding intrabdominal injuries or the necessity for surgical intervention and anesthesia [45]. Enteral nutrition is advised after shock resuscitation in unstable patients. Patients with abdominal trauma who received early enteral nutrition exhibited improved clinical outcomes, including reduced infectious complications and shorter hospital stays [46]. The timing of feeding initiation in patients with concurrent abdominal injuries should be determined by the treating surgeon and ICU specialist [46].

In cases of cerebral resuscitation, brain-injured patients may require continuous infusion of narcotics and sedation to offer analgesia, prevent increases in intracranial pressure associated with patient discomfort, agitation, or coughing, and decrease cerebral metabolic rate of oxygen consumption [47]. Moderate to high sedation is necessary for TBI patients complicated by seizures. Sedative agents can lead to dose-dependent cardiovascular depression, necessitating vasopressor support to maintain cerebral perfusion pressure. This raises the question among clinicians: is enteral feeding safe for patients on vasopressors? According to available data, a dose of 0.3ug/kg/min norepinephrine or its equivalent is considered safe for providing enteral nutrition. It is also recommended to gradually advance trophic feeds and monitor for any signs of feeding intolerance [48].

Delayed gastric emptying is a frequently observed complication in patients with head injuries. The gastric emptying half-life is more than doubled in patients with moderate to severe TBI. This condition can persist for up to two weeks following the trauma [49].

The precise mechanism behind the effects discussed in the previous text is not fully understood, but it is believed to be linked to increased pressure within the skull, changes in the body's natural hormone and chemical mediators, and dysregulation of the autonomic nervous system. However, there is a lack of consensus and published research on the high prevalence of delayed gastric emptying compared to the average population in the Intensive Care Unit (ICU).

It is important to acknowledge that different populations and types of injuries may present varying nutritional risks. Traumatic Brain Injury (TBI) admissions to the ICU can result from various causes, including falls related to drug or alcohol abuse, suicide attempts, and a higher incidence of accidents among the elderly population. Patients with these different causes of TBI may have a higher nutritional risk upon admission compared to those with TBI caused by road traffic collisions [50].

The role of the critical care dietitian in the nutritional support team, working alongside the intensive care physician, cannot be underestimated. The team must ensure that the patient's nutritional intake is monitored and that targets are met according to established standards. It is crucial to take appropriate measures to prevent excessive cumulative caloric and protein deficits, as these can increase mortality rates [50-58]. Furthermore, a significant challenge in managing nutrition among patients with severe TBI is the lack of up-to-date data and robust Randomized Controlled Trials (RCTs) or systematic reviews in this field. The absence of reliable data makes it difficult for healthcare providers to develop disease-specific and effective nutritional interventions. The deficiency in nutrition data for severe TBI highlights the need for further research to improve and provide comprehensive nutritional support.

Conclusion

In the critical care setting, feeding should be initiated as soon as possible once the patient is stable in terms of their hemodynamics and has a functioning gastrointestinal tract. Enteral nutrition is preferred over parenteral nutrition whenever possible. The calorie requirements should be tailored to each patient based on their demographic characteristics, comorbidities, severity of trauma, and phase of illness.

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