Nutrition therapy in the optimisation of health outcomes in adult patients with moderate to severe traumatic brain injury: Findings from a scoping review

Running Title: Nutrition therapy in TBI: A Scoping Review

Abstract

Introduction: Patients who have sustained traumatic brain injury (TBI) have increased nutritional requirements yet are often unable to eat normally, and adequate nutritional therapy is needed to optimise recovery. The aim of the current scoping review was to describe the existing evidence for improved outcomes with optimal nutrition therapy in adult patients with moderate to severe TBI, and to identify gaps in the literature to inform future research.

Methods: Using an exploratory scoping study approach, Medline, Cinahl, Embase, CENTRAL, the Neurotrauma reviews in the Global Evidence Mapping (GEM) Initiative, and Evidence Reviews in Acquired Brain Injury (ERABI) were searched from 2003 to 14 November 2013 using variations of the search terms 'traumatic brain injury' and 'nutrition'. Articles were included if they reported mortality, morbidity, or length of stay outcomes, and were classified according to the nature of nutrition intervention and study design.

Results: Twenty relevant articles were identified of which: 12 were original research articles; two were systematic reviews; one a meta-analysis; and five were narrative reviews. Of these, eleven explored timing of feed provision, eight explored route of administration of feeding, nine examined the provision of specific nutrients, and none examined feeding environment. Some explored more than one intervention. Three sets of guidelines which contain feeding recommendations were also identified.

Discussion: Inconsistency within nutrition intervention methods and outcome measures means that the present evidence base is inadequate for the construction of best practice guidelines for nutrition and TBI. Further research is necessary to elucidate the optimal nutrition therapy for adults with TBI with respect to the timing, route of administration, nutrient provision and feeding environment. A consensus on the ideal outcome measure and the most appropriate method and timing of its measurement is required as a foundation for this evidence base.

Keywords: Brain injury, nutrition intervention, trauma

Introduction

Traumatic brain injury (TBI), defined as an alteration in brain function or brain pathology resulting from an external force, is a pressing public health issue, with the World Health Organisation estimating that TBI will be the most prevalent cause of death and disability globally by 2020[1-3]. An estimated 10 million cases of moderate to severe TBI (leading to mortality or hospitilisation), occur worldwide each year[3]. Interventions that aim to enhance and improve the speed and extent of recovery from head injury are needed.

Nutrition-based interventions have the potential to enhance recovery and was identified by the Brain Trauma Foundation in 2007 as a priority research area and one of 15 key intervention types likely to influence outcomes in TBI patients[4]. *Nutrition support* is defined as the provision of additional nutrition via the parenteral (non-gastrointestinal route direct to the blood stream), or enteral route (via the nasal route using a nasogastric, nasoduodenal, or nasojejunal tube, or directly through the abdomen using a gastrostomy, gastrojejunostomy, or jejunostomy feeding tube)[5]. *Nutrition therapy*, which also includes the oral route, goes beyond nutrition support as a component of medical treatment aimed at maintaining or restoring optimal nutrition status and health[5]. In addition to the usual difficulties associated with the provision of nutrition therapy to critically-ill patients, optimal nutrition therapy in patients with moderate to severe TBI is made more complex by some unique physiological challenges.

Unique post-TBI metabolic changes result in an increase in energy requirements that can vary between 87% to 200% above usual values, extending up to 30 days post-injury[6]. This hypermetabolic response is thought to result from an increased production of corticosteroids, counter-regulatory hormones such as epinephrine, norepinephrine and cortisol, and pro-inflammatory mediators and cytokines such as interleukin-1 (IL-1), IL-6, IL-12, tumour necrosis factor-alpha (TNF-α), and interferon-gamma[7-10]. Whether these inflammatory markers can be used diagnostically to predict the influence of specific interventions on long-term outcomes is yet to be determined, but markers that correlate with the severity of disease and demonstrate prognosis are being sought[8,11]. Hypermetabolism can lead to the hypercatabolism of macronutrients, resulting in negative nitrogen balance, and substantially increased energy and protein requirements[6, 12, 13]. Hypercatabolism coupled with immobility can lead to an increased risk of malnutrition in the severely ill[14]. Nutritional requirements are further elevated by wound healing in cases of TBI with multi-trauma[15]. In one of the few studies on this topic, Krakau and colleagues demonstrated that approximately 68% of patients show signs of malnutrition within two months of head injury[16]. Dhandapani and colleagues showed that malnutrition has undesirable consequences with poor Glasgow Outcome Scale (GOS) at six months post-injury[17].

The difficulties in meeting increased nutrition requirements in TBI may be compounded further by dysphagia, gastrointestinal intolerance due to gastroparesis, fasting pre-surgery, and medication complications[6, 18, 19]. Post-traumatic amnesia, a state of altered consciousness associated with the recovery process, often results in inadvertent removal of feeding tubes and food refusal[12]. In many hospitals, nursing staff lack the capacity to provide the amount of assistance sufficient to ensure that the most difficult TBI patients get the nutrition they need[20, 21].

Although it is clear that increased nutrition is required following TBI, it is less evident which aspects of nutrition therapy lead to better outcomes. A systematic review of publications between 1993 to 2003[22] examined the evidence for effects of different timing, content, and method of administration of nutritional treatment on early and long-term clinical outcomes in patients with moderate to severe TBI. The reviewers concluded that the evidence base for determining the effect of nutrition support is insufficient, particularly in the post-injury phase[22,]. Three other systematic reviews[23-25] on nutrition therapy in TBI were published in 1996, 2000, and 2002 however these have since been updated[26, 27], but not synthesised. Since these reviews were published (the last in 2007), the influence of nutrient delivery in TBI, specifically immunonutrients, has emerged as an area of scientific interest. The extent of research and best practice with regards to nutrient provision in TBI is unknown, and questions regarding optimal timing of introduction of feeding, rate of achievement of nutrient targets, method of nutrient delivery, and feeding environment, remain.

The aim of the current scoping review was to summarise the current literature in the area of nutrition therapy and TBI, and to investigate the influence of nutrition therapy on outcome measures of mortality, morbidity (measured using Glasgow Coma Scale (GCS), Glasgow Outcome Scale (GOS), Acute Physiology And Chronic Health Evaluation II (APACHE II)), and length of hospital/Intensive Care Unit (ICU) stay, most commonly collected in the moderate to severe TBI population. The objective of the scoping review was to address the impact of four areas of nutrition therapy: 1) timing of feed provision; 2) route of administration of feeding; 3) the type of nutrients provided, including immunonutrients; and 4) the feeding environment.

Methods

Scoping reviews aim to identify and describe evidence in broad topic areas, such as nutrition therapy following TBI, that encompass a range of interventions and outcome measures. Like systematic reviews, they should include a comprehensive search and reproducible transparent methods for inclusion, evaluation, analysis and reporting. However, unlike systematic reviews, they usually focus on breadth of research activity and reported findings, rather than detailed independent quality appraisal and meta-analysis that are features of high quality systematic reviews of much more focused questions[28].

The current review focuses on moderate to severe TBI in adults given the highest prevalence rates in the adult population[3]. The causes, complications, and management associated with brain injury tend to differ between adult and paediatric patients, and much of the published research has been conducted separately on these populations, hence data reviewed included adult populations only[29]. Mild traumatic brain injuries do not always result in hospitilisation so studies which focused on this condition have less relevance for nutrition therapy and are therefore not included here. Given the unique needs of the traumatic brain injured patient we have excluded studies exploring other injuries that influence metabolism such as burns[30].

<u>Search Strategy:</u>

Articles were identified through a search of the following databases from 2003 to November 14, 2013: Medline and Cinahl via Ebsco, Embase via Scopas, and Cochrane Central Register of Controlled trials (CENTRAL). The search terms used combined two strings to include either TBI or brain injur* or brain damage* or brain trauma* or head injur* or head trauma* or craniocerebral trauma* or craniocerebral injur* or craniocerebral damage* or neurotrauma* or neuroinjur* AND nutri* or diet* or feed or feeding* or food* or cataboli*. Articles including the following search terms were excluded: stroke, paediatric*, pediatri*, infant*, and animal*. Appropriate truncation was used to account for plural words. The Neurotrauma reviews of the Global Evidence Mapping (GEM) Initiative and Evidence-Based Review of Moderate to Severe Acquired Brain Injury (ERABI) databases were also searched for nutrition and traumatic brain injuries[31, 32]. Databases were only searched for articles published from 2003 onwards given a systematic review conducted at this time provided a comprehensive review of the evidence[22], and several prior systematic reviews have been updated since 2003[23-25]. Reference lists of all included articles were also searched.

<u>Selection Process:</u>

Abstracts of articles identified in the search were screened according to inclusion/exclusion criteria. Inclusion criteria were: (1) studies of adults (aged ≥16 years); (2) moderate or severe traumatic brain injury as defined as GCS score 3-13; (3) description of a type of nutrition support or therapy; (4) at least one of the following defined outcome measures of TBI: mortality, change in GCS, GOS, or APACHE II score, or ICU or hospital length of stay (LOS). Studies were excluded if: (1) they were published in a language other than English; (2) the intervention was in children or animals; (3) they had a sample size of one patient; (4) other injuries included a direct insult to gastrointestinal tract or other conditions resulting in increased systemic response e.g. burns; (5) they were published prior to 2003; (6) they did not include at least one of the stated outcomes; or (7) results for TBI patients were not separated from those of other patients. Several reviews were also identified. These were only included if the main focus was nutrition therapy for TBI to demonstrate the breadth of published research. Duplicates were removed at the abstract review stage. In cases where the relevance of the article was unclear from the abstract, the full text article was retrieved. Articles investigating increased metabolism and gastrointestinal intolerance were excluded as they did not demonstrate the effect of nutrition therapy on the defined outcome measures (Figure 1).

Data was extracted from articles according to: (i) timing of feed provision; (ii) route of administration of feeding; (iii) type of nutrients provided including kilojoules, macronutrient, micronutrient, or immunonutrient provided; and (iv) feeding environment using a standardised form adapted from a combination of scoping review methodology papers and published scoping reviews[28, 33-36]. A different data extraction criterion was used for the included narrative reviews developed from the previous form. Guidelines for nutrition therapy were collected through reference checks and web searches using the same search terms, and analysed separately in order to extract the most relevant information. Articles were classified according to the Australian National Health and Medical Research Council (NHMRC) levels of evidence criteria, which are similar to international classifications[37].

Results:

The initial database search identified 1,574 unique articles within individual databases. After 142 duplicates across databases were removed, 1,432 articles remained. Title and abstract screening led to the retrieval of 230 potentially-relevant articles for assessment. One article was identified from a previous Google search and included in the analyses. Separate searches of the GEM and ERABI databases found two studies that met inclusion criteria. Seven articles were identified for retrieval from a search of reference lists, however these were all excluded after the abstract review stage as they did not meet the inclusion criteria for the population group. After full text review, 20 articles (two systematic reviews, one meta-analysis, five narrative reviews, and the remainder original research articles) were included in the scoping review. A narrative review was defined as an article that reviewed the literature without the use of specific systematic collection or collation of data and was mainly descriptive in nature. The most common reason for excluding articles was the lack of a clear description of the nutrition prescription (Figure 1). Other excluded articles contained only a small section on TBI, did not present data separately from other conditions, or did not report the defined outcome measures. No other scoping review published in the area of nutrition therapy following TBI was identified.

The number of articles on each topic are shown in Figure 2. ‘Timing of feed provision’ included articles exploring early versus delayed initiation of feeding; ‘Route of administration of feeding’ included articles discussing the route of delivery of nutrition therapy (e.g. enteral versus parenteral, gastric versus jejunal); studies that examined the provision of specific nutrients on TBI (energy, protein, fatty acids, probiotics, micronutrients, and immunonutrients) were categorised under the heading of ‘Type of nutrients provided’. Some articles addressed more than one topic and were included under more than one heading. Feeding environment, defined as the setting in which provision of nutrition therapy takes place, was an aim of this search however no articles meeting the criteria were revealed in the search.

Of the 20 identified papers, eight were classified as review articles: two were systematic reviews; one a meta-analysis; and five were narrative reviews, that is, they reviewed the literature without the use of specific systematic collection or collation of data and were mainly descriptive in nature.

Primary Research Articles:

Timing of feed provision:

The five primary research studies that examined the impact of timing of initiation of feeding on the defined outcome measures are summarised in Table 1. One was an RCT[38], three were cohort studies[39-41], and one a case series[42]. Early versus delayed feeding was defined in each article as: within 48 hours[38, 40]; by day three[42]; three versus four to seven versus greater than seven days[39]; and five versus seven days[41]. The RCT[38] found no difference on mortality rate of early versus delayed feeding, while all three cohort studies[39-41] found a positive influence on mortality. A positive relationship between early feeding and reduced LOS in hospital and ICU was found in the case series that assessed LOS[42]. One cohort[39] explored the effect of timing on GOS demonstrating a positive influence on GOS at three, but not at six, months. The case series[42] found that timing had no effect on GCS at time of discharge.

Route of administration of feeding:

Three RCTs[43-45] explored the influence of feeding route on the defined outcome measures as shown in Table 1. One of these explored parenteral versus enteral feeding[43] and the other two examined transpyloric versus gastric feeding[44, 45]. Two of the three RCTs explored the influence of route on mortality, one reporting no difference in mortality between parenteral and enteral[43,] and the other finding no difference between transpyloric and gastic[44]. All three RCTs concluded that the route of feeding had no impact on LOS in ICU[43-45], and two reported no impact on LOS in hospital[44, 45]. No original research study was found that used GOS as an outcome.

Type of nutrients provided:

As summarised in Table 1, five primary research studies (four RCTs[46-49], and one cohort study[41]) considered the effect of specific nutrient provision on TBI outcomes. Studies investigating the addition of glutamine and branched-chain amino acid (BCAA)[46], probiotics[48], or immunonutrient-rich enteral nutrition[49], found no impact on mortality. Hartl and colleagues demonstrated that every 10kcal/kg decrease in energy increased mortality by 30-40%[41]. A reduction in ICU LOS was shown with the provision of probiotics delivered nasogastrically[48], and a glutamine-probiotic combination[47], but not with a glutamine-BCAA combination[46].

Feeding environment:

No articles exploring the influence of feeding environment, such level of feeding assistance provided or ward versus dining room, on outcome measures were found. All studies focused on the acute care setting, in particular nutrition therapy in the intensive care unit, and no identified studies explored nutrition during the rehabilitation phase or until nutrition treatment is no longer required.

Review Articles:

Timing of feed provision:

Two systematic reviews[26, 27], one meta-analysis[50], and three narrative reviews[51-53] examined the impact of timing of initiation of feeding on the defined outcome measures as summarised in Table 1. One systematic review[26] and the meta-analysis[50] concluded a positive influence of early versus delayed feeding on mortality, with the meta-analysis showing significant reduction of mortality rate with early feeding[50]. The meta-analysis concluded that timing of feed provision had no significant difference in ICU LOS[50] in contrast to that found in the case-series by Vitaz and colleagues[42]. Two of the reviews explored the effect of timing on GOS: the systematic review concluded that early feeding improves GOS at three but not six months[27]; and the meta-analysis concluded that early feeding resulted in a significantly lower risk of poor outcome however time points of GOS measurement were not stated[50]. The three narrative reviews each provided a recommendation for early initiation of feeding within 24-72 hours[51], 48 hours[53], and 72 hours[52], using other narrative reviews, articles using different modes of feeding as well as timing, or the practice guidelines to support these recommendations[27, 56, 57].

Route of administration of feeding:

One systematic review[26], one meta-analysis[50], and three narrative reviews[51-53] explored the influence of feeding route on the defined outcome measures as shown in Table 1. Both the systematic review and the meta-analysis explored parenteral versus enteral feeding on mortality[26, 50]. The systematic review found that enteral feeding increased the relative risk for mortality above parenteral feeding[26], and the meta-analysis found a trend toward lower mortality rate with parenteral nutrition[50]. Only the meta-analysis reported on GOS, showing a trend towards a reduction in the relative risk of poor outcome with parenteral nutrition[50]. However, all three narrative reviews recommended enteral nutrition over parenteral feeding[51-53], unless in the case of prolonged gastrointestinal dysfunction[52] or when enteral is unable to meet nutritional goals[51]. While one of these narrative reviews referenced the Canadian Clinical Practice Guidelines[51], the other two narrative reviews provided no references to support these recommendations[52, 53].

Type of nutrients provided:

As summarised in Table 1, one systematic review[27] and three narrative reviews[51, 54, 55] considered the effect of specific nutrient provision on TBI outcomes. The systematic review found a non-significant trend for zinc supplementation and reduced mortality[27] as supported by one narrative review[54]. Both Cope[54] and Vizzini[51] conclude that zinc supplementation can improve GCS scores, however the optimal dose is currently unknown. Only one narrative review[55] discussed the effect of immune-enhancing diets, concluding that a high-protein formula enriched with L-arginine, glutamine, and omega-3 fatty acids for the first 7-10 days post-injury can reduce hospital LOS.

Given no studies were found on the impact of feeding environment on TBI outcomes it is unsurprising that no reviews addressed this.

Guidelines:

Three practice guidelines for use in the critically ill or trauma patient were identified and included[27, 56, 57]. The Guidelines of the Brain Trauma Foundation in the USA focused specifically on nutrition in severe TBI[27]; The Eastern Association for the Surgery of Trauma in the USA focused on general trauma which included head injury and burns[57]; and the Canadian Critical Care Practice Guidelines in Canada focused on the critically ill population with some head injury specific recommendations[56]. All guidelines made recommendations on the common areas of timing of feed initiation (early versus delayed), administration of feeding (gastric versus jejunal versus parenteral), and nutrient provision (immune-enhancing, and macronutrient composition)[27, 56, 57]. There was a recommendation for early initiation of enteral feeding (within 24-48 hours of admission) over parenteral nutrition or delayed feeding[56, 57] and a further recommendation for full energy requirements to be met by day seven post-injury[27]. Two sets of guidelines provided a recommendation on overcoming barriers of nutrition therapy in TBI; one set of guidelines recommended using post-pyloric feeds if gastric feeding is not tolerated within 48 hours of injury[56], and another set highlighted the importance of implementing strategies to optimise delivery of nutrients such as starting at target rate, jejunal feeding, and higher thresholds for gastric residual volumes[57]. Importantly, all guidelines stated that there was insufficient data to support recommendations regarding macronutrient intake, and immune-modulating or enhanced nutrition including omega-3 fatty acids, glutamine, arginine, nucleotides, antioxidants, and provision of additional nutrients such as zinc and selenium[27, 56, 57].

Discussion

This scoping review examined the evidence on nutrition therapy in TBI, identifying a range of research topics previously not captured by systematic reviews or meta-analyses, including provision of nutrients and immunonutrition. No published research about the feeding environment was found. Nutrition therapy appears to be an under-researched area and evidence that does exist is equivocal. Practitioners therefore lack evidence-based guidance on the optimal timing of initiation or administration of feeding, or nutrient provision, in terms of improving mortality or morbidity outcomes. The few relatively small trials that have been conducted may have been underpowered to show significant differences, and larger, high quality trials may be needed.

The two identified systematic reviews covered more than one aspect of nutrition therapy, such as timing and administration[26], and the ability of nutrition therapy to meet requirements[27]. The combination of numerous research questions into a single review may demonstrate the limited evidence available to complete a systematic review on a single aspect of nutrition care. Many of the conclusions in these reviews are based on the finding of only one or two studies. The meta-analysis published by Wang and colleagues in March 2013 provides a synthesis of RCTs and prospective cohort studies investigating timing, route, and nutrient provision in TBI however it inadequately reflects the breadth of research conducted[50].

Three sets of guidelines were identified that provide recommendations on nutrition therapy in TBI[27, 56, 57], however the recommendations were based on small numbers of studies of both questionable quality and relevance. Some of the practice recommendations were supported by one or two studies only, many of which were conducted in the 1980s under different medications and technological regimes, with inadequately defined outcome measures and small patient numbers. The guidelines were found to be limited in the scope of practice covered, or generalised to the critically ill or general trauma population despite the unique needs of the TBI patient being well documented.

A major finding from the current scoping review is the inconsistency of methods used in nutrition studies, particularly in relation to outcome definitions. This current review included studies that had mortality, morbidity (using GCS, GOS, or APACHE II), or ICU or hospital LOS as an outcome, however inconsistencies in the way these outcomes were measured is a limitation previously recognized to affect likely results[58]. Some reviews failed to define how outcomes, such as neurological outcome, were measured in the included studies[27]. Different studies used different protocols to measure the same outcome, for example the extent of disability was measured using GCS, GOS, and APACHE II. In addition, there was often not one clear primary outcome measure used. Time points of outcome measurements varied between studies; for example morbidity was measured between two weeks[41] and six months[39] post-injury depending on the trial, which is likely to have a significant impact on results, given the severity of injury and length of stay in ICU and hospital. Most studies did not explore mortality beyond three weeks post-injury. Many articles which were included did not use mortality or morbidity as an outcome measure, hence the safety of the intervention may be unknown. Anthropometric data were not routinely collected in the included studies and such intermediate outcomes could be useful in future studies. Further consensus of the ideal outcome measures, and the most appropriate method and timing of their measurement, is required to enable comparison between studies and synthesis of the evidence.

Clearer definitions of threshold values of continuous measures are also required for interventions since inconsistencies in classifications of hyperglycaemic and feeding intolerance were found between studies[44, 45]. Methods to determine nutritional requirements varied greatly between studies. Many studies compared early versus delayed feeding but the definition of timeframe that constituted early or delayed was inconsistent, making comparisons difficult. The early feeding classification varied from 48 hours[38, 40], day three[39], day four[42], or day five post-injury[41], whilst variations in delayed feeding included meeting requirements after day four[38, 42], day seven[39, 40], or day nine post-injury[26, 27]. Many of the clinical studies explored similar nutrients, such as glutamine, probiotics, and branched chain amino acids, however comparisons between studies was difficult as these were included in different combinations and doses[47-49].

Follow-up assessment periods varied between studies, with nine studies[27, 38, 42-44, 47-50] not stating when follow-up was conducted. All studies focused on the acute hospital admission, generally classified as the first two weeks post-injury, and only one of the systematic reviews[26] and one of the included studies[39] extended past this acute phase to examine outcome measures up to six months post-injury (rehabilitation phase). The provision of nutrition therapy in rehabilitation was therefore not able to be examined. This leads to a lack of evidence to support management guidelines in the later post-injury stage, where many of the complications of TBI persist. Given the changing nature of the brain injury on inflammation and nutritional requirements, further research to guide best practice guidelines through all phases of care including intensive care, acute ward, and rehabilitation, is required.

The current scoping review was limited to articles published in English and, as such, relevant studies in other languages may have been missed. Furthermore, systematic reviews were relied on for the results of studies published before 2003, which may have resulted in incomplete reporting of the literature. Nevertheless, these findings from the current scoping review demonstrate that the evidence base to support best practice guidelines for nutrition therapy in moderate to severe TBI patients is limited in scope and methodology. While early initiation of nutrition support can improve patient outcomes, the field is characterised by small study sizes, and inconsistencies between outcome measures and nutrition intervention methodologies which prevent meaningful data synthesis on which to base recommendations. Further high quality, adequately powered clinical trials specific to TBI, with enhanced consistency between definitions and protocols, are essential to improve the evidence-base necessary for safe and effective recommendations for nutritional management of patients with moderate to severe TBI. Internationally accepted definitions of outcomes of mortality, Glasgow Outcome Scale, and nutritional status (e.g. muscle mass and weight) need to be established and applied. Further research is particularly required on the influence of the feeding environment and macro- and micro-nutrient provision on TBI outcomes in the medium to long term. Until further high quality research is available, nutrition therapy should be initiated to meet full caloric requirements by day seven post-injury using strategies to optimise the delivery of nutrients and overcome physiological challenges as determined by experienced clinical judgment, taking into account the individual requirements of the patient.

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