


BMJ Open Immunonutrition for traumatic brain injury in children and adolescents: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Traumatic brain injury (TBI) is the leading cause of paediatric trauma death and disability worldwide. The ‘Guidelines for the Management of Severe Traumatic Brain Injury (Fourth Edition)’ recommend that nutritional goals should be achieved within 5–7 days of injury. Immune-enhancing nutrition or immunonutrition, referring to the addition of specialised nutrients, including glutamine, alanine, omega-3 fatty acids and nucleotides, to standard nutrition formulas, may improve surgical outcomes in the perioperative period. However, the role of immune-enhancing nutritional supplements for patients with paediatric TBI remains unclear. We will conduct a systematic review to determine the efficacy and safety of immunonutrition for patients with paediatric TBI and provide evidence for clinical decision-making.

Methods and analysis Studies reporting immune-enhancing nutrition treatments for patients with paediatric TBI will be included. Outcomes of interest include the length of hospital stay, wound infections, all-cause mortality, non-wound infection, including pneumonia, urinary tract infection and bacteraemia, and the reports adverse events. Duration of follow-up has no restriction. Primary studies consisting of randomised controlled trials (RCTs) and non-RCTs will be eligible for this review, and only studies published in English will be included. We will search the Medline, Embase and Cochrane Library databases from their inception dates to January 2020. We will also search clinicaltrials.gov and the WHO International Clinical Trials Registry Platform for additional information. Two reviewers will independently select studies and extract data. Risk-of-bias will be assessed with tools based on the Cochrane risk-of-bias criteria and Newcastle-Ottawa Quality Assessment Scale. A meta-analysis will be used to pool data when there are sufficient studies with homogeneity. Heterogeneity of the estimates across studies will be assessed; if necessary, a subgroup analysis will be performed to explore the source of heterogeneity. The Grades of Recommendation, Assessment, Development and Evaluation method will be applied to assess the level of evidence obtained from this systematic review.

Ethics and dissemination The proposed systematic review and meta-analysis will be based on published data, and thus ethical approval is not required. The results of this review will be published.

Strengths and limitations of this study

- This systematic review will determine the efficacy and safety of immunonutrition for paediatric traumatic brain injury (TBI) patients and provide some evidence for clinical decision-making.
- Subgroup analysis (eg, the severity of TBI and type of immunonutrition) will make it possible to identify the efficacy and safety of specific immunonutrition nutrient for certain characteristics of patients with paediatric TBI.
- The potential limitation of this systematic review could be the heterogeneity of studies in exposure of interest and restriction to studies in English language.

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INTRODUCTION

Traumatic brain injury (TBI) is the leading cause of paediatric trauma death and disability and affects up to 280 out of 100 000 children worldwide.¹ In the USA alone, TBI affects 475 000 children a year and causes more than 2600 deaths, 37 000 hospitalisations and 435 000 emergency department visits.^{2–3} Approximately 5000 children are disabled due to TBI every year. In addition, TBI costs approximately \$2.6 billion a year for treatment.⁴

In a prospective series study, 98% of children in the emergency departments had a Glasgow Coma Scale (GCS) score of 15, indicating that most head injuries were mild.⁵ However, approximately 75% of children with multiple injuries have a TBI, and almost 80% of traumatic deaths are related to TBI.^{6,7} In retrospective series studies, mortality rates ranged from 17% to 33% in children with severe brain injury.^{8,9} TBI is the most common cause of trauma-related death and disability in developed countries.¹⁰ Despite the higher



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survival in children with TBI, disability is significant, with the functional long-term outcome being associated with the initial injury severity.^{10–12}

Nutrition support refers to enteral or parenteral provision of calories, protein, electrolytes, vitamins, minerals, trace elements and fluids. The ‘Guidelines for the Management of Severe Traumatic Brain Injury (Fourth Edition)’ recommend that nutritional goals should be achieved within 5–7 days of injury and that enteral nutrition should be considered to reduce the incidence of ventilator-associated pneumonia.¹³ There is some evidence that early enteral nutrition may reduce the incidence of pneumonia¹⁴ as well as mortality¹⁵ in patients with TBI, although a randomised controlled trial (RCT) did not demonstrate a reduction in complications.¹⁶ Furthermore, in the perioperative period, immune-enhancing nutrition treatment or the use of ‘immunonutrition’, referring to the addition of specialised nutrients, including glutamine, alanine, omega-3 fatty acids and nucleotides, to standard nutrition formulas, may improve surgical outcomes.¹⁷

How an immunonutrition intervention might work?

TBI has long been recognised as the leading cause of traumatic death and disability.¹ Surgical and intensive care unit management have made tremendous advances in reducing mortality of TBI. However, neuroinflammation, excitatory amino acids, free radicals and ion imbalance is a prolonged pathogenic process in patients with TBI.¹⁸ Few therapies directly alter these underlying processes to improve the outcome of patients with TBI. However, immunonutrition, even in a prophylactic setting, may provide nutrients for the brain to begin the healing process following TBI.^{18–23}

The most common immunonutrients are arginine, glutamine, omega-3 fatty acids and nucleotides.²⁴ Arginine is the most common immune-enhancing nutrient given to surgical patients. It is a non-essential amino acid with a role in the synthesis of nucleotides, polyamines, nitric oxide and proline. Arginine may stimulate lymphocyte function and improve wound healing. Glutamine, also an amino acid, is a fuel for rapidly dividing cells in the body, particularly enterocytes and colonocytes. The addition of omega-3 fatty acids to enteral nutrition feeds reduces proinflammatory mediators in stressed patients and may reduce infections. The role of immune-enhancing nutritional supplements remains unclear. There is insufficient high-quality evidence to suggest any specific supplementation for all surgical patients.²⁴

Why it is important to perform this review?

Malnutrition in hospitalised patients is well documented, with an incidence of up to 50% in some populations.^{25–27} Nutritional support may be suitable for malnourished patients who need surgical treatment or for healthy patients who are undergoing major surgery and are expected to be recovering gastrointestinal function for a long time. However, it may be difficult to choose an

appropriate nutrition formula. In particular, the use of immunonutrition has aroused many controversies.²⁴ Some studies have demonstrated that there was some benefit but no effect on survival in surgical patients.^{17 28–35} Some meta-analyses have shown that immunonutrition could reduce infectious complications and shorten the length of hospital stay but had no effect on mortality.^{29–32 36–39} However, some multicentre randomised studies have reported conflicting results,⁴⁰ immunonutrition may be associated with high mortality in patients with severe sepsis.⁴¹ The ‘Guidelines for the Management of Severe Traumatic Brain Injury (Fourth Edition)’ were unable to make a generalised recommendation for their use,¹³ the ‘Guidelines for the Management of Pediatric Severe Traumatic Brain Injury (Third Edition),’⁴² based on one RCT from 2006,⁴³ do not recommend immunonutrition for use. Considering that there are some new evidences on this topic,^{44 45} several studies have shown that the potential of immunonutrition to reduce cytokines, increase antioxidant indices and improve functional outcome, colonisation and infection rates in patients with TBI.^{19 21 43 44 46–48}

One systematic review and meta-analysis of prospective studies showed that immune-enhancing formulas reduce infection rate, but the participants in the original study were adult patients with TBI.⁴⁷ Briassoulis *et al* suggested that immunonutrition showed a trend to improve colonisation and infection rates in critically ill children but required some changes in immune enhancing formulae for specific age populations.⁴⁶ These overall results appear promising that immunonutrition may benefits for patients with paediatric TBI. Evidence is needed to confirm these findings and determine the optimal agents in patients with paediatric TBI. The purpose of this systematic review is to determine the efficacy and safety of immunonutrition for paediatric TBI patient.

METHODS

Methods and analysis

This systematic review and meta-analysis will be conducted according to the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0),⁴⁹ and the reporting of our study will be based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.⁵⁰

Objective

To determine the efficacy and safety of immunonutrition for patients with paediatric TBI.

Eligibility criteria

Participants

Studies of patients with paediatric TBI, aged from 0 to 18 years old, are eligible for this review. There are no restrictions on the basis of nationality or on the stage or grade of TBI.

Intervention

The intervention in this review is immunonutrition treatment. Immunonutrition treatment refers to enteral or

parenteral nutrition supplementation with arginine, glutamine, non-essential fatty acids, branched chain fatty acids and nucleotides. Any type of immunonutrition is valid. Regardless of the start and end times, dose, frequency, duration and combination of immunonutrition.

Control

The controls are patients with paediatric TBI of the same age and severity of TBI who receive standard feeding without immunonutrients.

Studies

We will include reports on the efficacy and safety of immunonutrition for patients with paediatric TBI from RCTs and non-RCTs (cohort studies and case-control studies). There is no limitation regarding the number of participants. Only studies published in English will be included.

Outcomes

We will evaluate the following outcomes in this review, but we will not use them as a sole basis for excluding studies. Primary outcomes include the length of hospital stay and wound infections. Secondary outcomes will include the following: all-cause mortality, non-wound infection, including pneumonia, urinary tract infection and bacteraemia, and reports of adverse events. The adverse events will include any type of reported adverse event. The duration of follow-up will not be restricted.

Information sources

We will search the Medline and Embase databases and the Cochrane Library from their inception to January 2020. We will combine both MeSH and free-text terms to identify relevant articles. An information expert (YX) will develop our search strategies. We will also search clinicaltrials.gov (<https://clinicaltrials.gov/>) and the WHO International Clinical Trials Registry Platform (<http://apps.who.int/trialsearch/>) for additional information. There will be no language restrictions. Meanwhile, we will use a manual search strategy to retrieve the relevant articles referred to by the retrieved publications.

Search strategy

The search will be performed using a combination of MeSH and free-text terms to identify relevant articles. Search words will be adopted for each database and will mainly include the following: immunonutrition, glutamine, arginine, omega-3 fatty acids, nucleotides, TBI and their synonyms. An example of the Medline search strategy is shown in online supplementary table 1. We will scan the reference lists of eligible studies and relevant review articles to identify any potentially eligible studies missed during our search. The Information expert will conduct non-systematic searches of Google Scholar to retrieve grey literature and other sources of potential trials.

Risk-of-bias assessments

The methodological quality of the included RCTs will be assessed independently by two researchers based on the Cochrane risk-of-bias criteria.⁴⁹ We will use the Newcastle-Ottawa Quality Assessment Scale to assess the risk of bias of cohort studies and case-control studies.⁵¹

Data extraction

All the records retrieved from the databases will be processed using EndNote X9 (Clarivate Analytics, UK). All extracted data will be stored in Microsoft Excel 2016 (Microsoft Corporation, USA). Two researchers will independently extract the following information from each eligible study: (1) general study characteristics: author name, year of publication, country, study design, trial registry number, number of participants and follow-up period; (2) patient characteristics: sex, age, ethnicity, patients' baseline information (type of brain injury (diffuse or focal or the initial), GCS or paediatric GCS score, intracranial pressure (normal, high or low, and the monitoring method), mechanical ventilation (yes or no, and duration) and nutritional status (clinical nutrition evaluation: sex-specific and age-specific body mass index or other assessment methods), if reported); (3) primary diseases; (4) interventions: details of the immunonutrient treatment and control group (eg, the start and end times, dose, frequency, duration and combination of immunonutrition); and (5) the outcomes: the length of hospital stay and wound infections. Secondary outcomes will include the following: all-cause mortality, non-wound infection, including pneumonia, urinary tract infection and bacteraemia, and adverse events. The adverse events will include any reports of adverse events, such as diarrhoea, nosocomial pneumonia, severe sepsis and brain herniation.

If the trials have more than two groups or factorial designs and appropriate multiple comparisons, we will extract only the information and data of interest reported in the original articles. If a trial has multiple reports, we will collate all data into one study. If a trial has reports from both [ClinicalTrials.gov](https://clinicaltrials.gov/) and journal publications, we will carefully check the data from these two sources for consistency. If the outcome data were reported at multiple follow-up points, we will use data from the longest follow-up. We will extract both the crude and adjusted estimates in non-RCTs.

Statistical analysis

The efficacy and safety of the administration of immunonutrients in patients with paediatric TBI aged 0–18 years will be assessed. We will record data on the number of participants for each outcome event by allocated group, the number of participants in compliance and the number of participants who were later thought to be eligible or otherwise excluded from treatment or follow-up. We will conduct analysis with intention to treat and per protocol analysis. These two analysis

methods are recommended by the Consolidated Standards of Reporting Trials recommendations.⁵²

We will conduct separate analyses for RCTs and non-RCTs. In the non-RCTs, we will report crude or adjusted estimates of treatment effect separately in two meta-analyses and report the confounding factors adjusted for. In both RCTs and non-RCTs, we will pool data with random-effects model when there are sufficient studies with homogeneity.⁵³ We will perform a meta-analysis to calculate ORs, risk ratios (RRs) or absolute risk differences (ARDs) in dichotomous data and mean differences in continuous data, as well as 95% CIs using the Mantel-Haenszel statistical method and inverse variance statistical method, respectively. If sufficient data are not available in the published reports or conference abstracts, we will contact the authors of the paper. If the raw data are not means and SD, the sample mean and SD will be estimated from the sample size, median, range and/or IQR.^{54 55}

We will assess heterogeneity using both the χ^2 and I^2 tests.⁴⁹ If heterogeneity is identified ($I^2 > 40\%$ ⁴⁹ and there are sufficient trials included in the review, we will analyse the possible reasons for the heterogeneity. We plan to investigate heterogeneity by the specified subgroups based on the type of immunonutrition supplements (ie, arginine, glutamine, non-essential fatty acids, branched chain fatty acids, nucleotides or other immunonutrition supplements), combination of immunonutrition supplements (yes or no), patient ethnicity, pre-existing malnutrition (yes or no), severity of TBI (mild, GCS score 13–15; moderate, GCS score 9–12; severe, GCS score <9), intracranial pressure (normal, high or low) and mechanical ventilation (yes or no). An analysis will be performed to assess whether the difference between the subgroups is statistically significant. However, if the number of studies is very small, the statistical power will have poor precision due to the between-study variance. In this case, we will add the separate effects to our manuscript. A sensitivity analysis will be performed by the type of study design (RCTs, cohort studies and case-control studies), excluding low-quality studies, trials recruiting participants with particular conditions or trials with characteristics different from the others. When an inconsistency is detected between the RR and ARD of the same outcome, we will explain the results based on the RR because the RR model is more consistent than the ARD model, particularly for an intervention aimed at preventing an undesirable event.^{49 56}

We will assess publication bias by examining funnel plots when the number of trials reporting the primary outcomes is 10 or more. All meta-analyses will be performed using the Review Manager (RevMan) software package V.5.3 (by the Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2014). All tests will be two-tailed, and $p < 0.05$ will be considered statistically significant.

We will use the Grading of Recommendations Assessment, Development, and Evaluation methodology to

rate the certainty of evidence as high, moderate, low or very low.⁵⁷ RCTs begin as high certainty evidence but can be rated down because of risk of bias, imprecision, inconsistency, indirectness and publication bias. If the limitation of the evidence is considered serious, the evidence is downgraded by one level; if the limitation of the evidence is considered very serious, the evidence is downgraded by two levels. Observational studies begin as low-quality evidence but can be rated upwards for a large magnitude of effect, a dose-response gradient or the presence of plausible confounders or other biases that increase confidence in the estimated effect.

Patient and public involvement

Patients and their families were not involved in setting the research question or the outcome measures, but they were intimately involved in the design, which helped to give our team much good advice regarding the design.

DISCUSSION

In this systematic review of immunonutrition for patients with paediatric TBI, we will conduct a comprehensive literature search and used objective criteria for study inclusion and methodological appraisal. Although many studies have shown that immunonutrition may be benefit for patients with TBI in healing process and functional recovery,^{18–23} immunonutrition may do more harm than good in patients with severe sepsis.⁴¹ The ‘Guidelines for the Management of Severe Traumatic Brain Injury (Fourth Edition)’ were unable to make a generalised recommendation for the use of immunonutrients.¹³ Besides, based on one RCT from 2006,⁴³ the Guidelines for the ‘Management of Pediatric Severe Traumatic Brain Injury (Third Edition)’ do not recommend immunonutrients for use.⁴² Because there are some new evidences on this topic, the conclusions about the efficacy and safety of immunonutrition for paediatric TBI children patients are inconsistent.^{43 44 46 58} There is no systematic review for this topic in child and adolescent TBI patients. It is difficult to make a definite decision in administration of immunonutrients for patients with paediatric TBI. It is necessary to find evidence to address these uncertainties. Taking this into consideration, it is very meaningful to carry out this systematic review to determine the efficacy and safety of immunonutrition in patients with paediatric TBI. The results of our review will indicate the efficacy and safety of immunonutrients in patients with paediatric TBI, which will provide a reference for decision-making regarding the utilisation of drugs, pharmaceutical care, procuring and storing of drugs, studying and developing preparations, reevaluation of drugs on sale and so on.

There are also some possible limitations of our review. First, there may be some heterogeneity across studies, as the study populations’ baseline for each trial and the

study design are heterogeneous. To explore the possible sources of heterogeneity, we will perform subgroup analyses. Second, only studies published in English will be included to overcome the language barrier. Thus, we may lose data published in other languages, which may cause publication bias to some extent. Third, we will perform further studies to address this question in the near future.

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Contributors RP and LingZ conceived the review protocol and drafted the manuscript. RP, HL, LinZ and ZB revised the study design. RP, HL, LY and XC participated in the design of the search strategy and data extraction data set. RP, HL and LinZ formed the data synthesis and analysis plan. In practice, RP and LingZ will monitor each procedure of the review and are responsible for the quality control. All authors critically revised the manuscript and approved the publication of the protocol.

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