Systematic Reviews

PROTOCOL

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Protocol for a systematic review and meta-analysis investigating the impact of continuous versus intermittent enteral feeding in critically ill patients

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Abstract

Introduction Enteral nutrition (EN) is the recommended nutritional support in most critically ill populations. When given by feeding tube, EN may be administered either continuously or intermittently. It is unclear which approach is superior in reducing gastrointestinal complications—such as diarrhea—and meeting nutritional targets. The main objectives of this systematic review and meta-analysis are to (1) determine whether continuous or intermittent enteral nutrition is associated with higher incidence of adverse gastrointestinal outcomes, including diarrhea, and (2) determine which feeding modality is associated with reaching nutritional goals.

Methods and analysis This systematic review protocol is reported in accordance with guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement. We will search MEDLINE, Embase, the Cochrane Library, and the World Health Organization (WHO) International Clinical Trials Registry (ICTRP) search portal for studies comparing continuous EN and intermittent EN in critically ill patients with no date or language restrictions. Studies will be screened, selected, and extracted independently and in duplicate. We will assess the risk-of-bias assessment using the Cochrane Collaboration's Risk of Bias (RoB) 2 tool. The primary outcome will include the incidence of diarrhea; secondary outcomes include other adverse GI outcomes (nausea, vomiting, abdominal pain, and constipation), as well as reaching nutritional goals, and length of ICU and hospital stay and mortality. We will pool data using a random-effects model and assess the certainty of the evidence for each outcome using Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology.

Ethics and dissemination Ethics approval is not required for this study as no original data will be collected. We will disseminate results through peer-reviewed publication and conference presentations.

Systematic review registration PROSPERO CRD42022330118.

Keywords Diarrhea, Intermittent feeding, Continuous feeding, Bolus feeding, Intensive care unit, Enteral nutrition, Gastrointestinal system

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Strengths and limitations of this study

- This systematic review protocol adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA) guidelines.
- This paper addresses a current gap in the literature, and the results from this work may inform future nutritional protocols in critical care.
- We developed the search strategy for this systematic review along with two experienced medical librarians.
- This review is limited to evidence from randomized controlled trials.
- This review may be limited by the restricted number of studies conducted on this topic, as well as potential high risk of bias.

Introduction

Rationale

The current European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines for nutrition in the ICU recommend enteral nutrition (EN) as the most effective form of feeding in critically ill patients who cannot receive at least 70% of their nutritional needs through oral feeding [1]. EN is a safer alternative to parenteral nutrition and is associated with a decreased risk of infectious complications [1], maintains GI tract integrity, and is less costly [2]. Enteral nutrition may be administered to a patient continuously (EN received continuously over 24 h) or through intermittently (EN received in scheduled doses with rest periods in between).

Recently, the *diarrhea: interventions, consequences and epidemiology in the intensive care unit* (DICE-ICU) study identified multiple risk factors for diarrhea, including the use of EN [3]. Diarrhea is described by the World Health Organization (WHO) as the passage of three or more loose or liquid stools a day [4]. Diarrhea is further subcategorized into three categories: acute watery diarrhea, acute bloody diarrhea, and persistent diarrhea. It may also be classified according to its etiology as inflammatory, secretory, or due to altered motility [5]. Diarrhea may result in fluid loss with consequent dehydration with the potential to progress to vascular collapse and hypovolemic shock and is associated with a myriad of electrolyte abnormalities, including but not limited to bicarbonate loss leading to metabolic acidosis, hypokalemia, and hypomagnesemia [6].

Reports of incidence of diarrhea in the ICU differ depending on the definition used; the DICE-ICU study found an incidence of 73.8% (95% *CI* 71.1–76.6) employing the WHO definition, 53.5% (95% *CI* 50.4–56.7) using the Bristol stool chart, and 37.7% (95% CI 34.9–40.4) using the Bliss Stool Classification System [3]. Diarrhea was found to be associated with an increase in intensive care unit (ICU) length of stay and hospital length of stay, as well as with a decrease in quality of life and complications including skin breakdown [3]. Although diarrhea is linked to both to enteral nutrition and worse clinical outcomes, it remains unclear whether continuous versus intermittent approaches to EN mitigate the risk of these outcomes or improve nutrition delivery. Previous studies on this topic have had conflicting or unclear results [7].

Objectives

In this review, we seek to investigate the effects of continuous versus intermittent enteral feeding on outcomes important to ICU patients, including GI outcomes (diarrhea, constipation, abdominal pain, nausea, and vomiting) and nutritional deficiencies. This has the potential to provide information that may reduce the incidence of diarrhea and other adverse outcomes in patients and inform ICU feeding protocols and clinical practice guidelines globally.

Methods

This protocol has been registered within the International Prospective Register of Systematic Reviews (PROSPERO) database (registration ID: CRD42022330118). This protocol is reported in accordance with guidance from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement [8].

Eligibility criteria

Types of studies

This systematic review will include randomized controlled trials (RCTs). We will exclude animal trials and conference abstracts.

Types of participants

The participants of studies included in this review will be restricted to adult patients (age 18 or older) who are receiving enteral nutrition and who are admitted to an ICU at the time of study enrolment. We will exclude pediatric studies due to this population's unique needs while receiving EN [9]. We will exclude studies that include subjects with preexisting conditions that independently contribute to adverse GI outcomes. These may include, but are not limited to, patients with active *Clostridioides difficile* infection and patients with existing GI disorders such as irritable bowel syndrome, inflammatory bowel disease, ostomy, and celiac disease.

Type of intervention

The studied intervention is intermittent EN, defined as administration of 200–400 mL of feed over 15–60 min at

regular intervals [10] or as defined by the author. We will not include studies that include administration of parenteral nutrition as part of the nutrition regimen.

Type of comparator

The comparator is continuous EN, defined as feed administered at a steady rate over the course of 12–24 h [10] or as defined by the author.

Outcome measures

Primary outcome

The primary outcome of interest in this review is the incidence of diarrhea in ICU patients. Diarrhea will be defined in this study according to the most recent definition of diarrhea created by WHO. Diarrhea is defined as the passing of three or more loose or liquid stools in a day [4]. We will consult the definition of diarrhea each selected study uses, and if necessary, we will adopt the author's definition of diarrhea if it differs from the WHO definition.

Secondary outcomes

Secondary outcomes of interest in this review include incidence of other GI intolerances including vomiting, nausea, abdominal pain and discomfort, and constipation. These will be defined according to the authors' definitions. We will also capture hospital length of stay, ICU length of stay, and mortality using the time frame selected by the author.

Information sources

Electronic sources

The literature search will be performed by an information specialist (KC) following PRISMA-S guidance [11], using a search strategy peer-reviewed by KD (Supplementary 1). The search strategy will be reviewed according to the methods described in McGowan, 2016 [12]. Published literature will be identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid, Embase (1974–) via Ovid, and the Cochrane Library via Wiley. The search strategy will consist of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The ICTRP search portal and ClinicalTrials.gov will be searched for reports of additional trials. The main search concepts will be intensive care and bolus or continuous feeding.

Methodological filters will be applied to limit the retrieval to reports of randomized controlled trials or systematic reviews/meta-analyses/health technology assessments. Trial report retrieval will be limited to the human population where possible but was not limited by publication date or language. Duplicate records will be removed between MEDLINE and Embase using Ovid default duplicate detection, with any additional duplicates identified and removed in Covidence.

Searching other relevant sources

The reference list of all studies selected for inclusion will be reviewed for any additional publications that may meet the inclusion criteria for this study. If any potentially relevant studies are identified, they will be screened using the same process as the other included studies to determine if they meet the inclusion criteria.

Data collection and analysis

Selection of studies

Two reviewers (L. S. A., A. M. C.) will independently review the title and abstract of each publication retrieved to determine which should be assessed further as a full-text review. For any citation selected as potentially relevant, the same reviewers will assess the full text for eligibility. At this stage, we will capture reasons for exclusion, and any discrepancies will be resolved by either consensus or review by a third independent reviewer (J. C. D.).

Data extraction and management

We will extract the frequency and details of the outcome data from each study. We will collect the year of publication, duration of intervention, location of study, and number of participants randomized of each study. We will also collect medical comorbidities, age, sex, and ethnicity of the participants. We will collect all data using a pre-piloted data extraction sheet created using Covidence [13].

Assessment of risk of bias in included studies

Two reviewers (L. S. A., A. M. C.) will independently assess risk of bias for each study. In cases of disagreement, resolution will be reached by consensus after discussion or by assessment completed by a third reviewer (J. C. D.). Risk of bias (RoB) in randomized trials will be assessed by using V.2 of the Cochrane RoB tool for RCTs (RoB 2) [14].

We will assess certainty of evidence for each outcome effect estimate using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) classification, which considers risk of bias, imprecision, indirectness, inconsistency, and publication bias in determining the certainty of the evidence [15].

Dealing with missing data

We will contact research authors for clarification when data is missing from publications selected for inclusion. In the case that this data is not obtainable, we will

incorporate this into the risk-of-bias assessment and GRADE certainty rating.

Assessment of reporting biases

We will use funnel plots to assess the risk and presence of publication bias. These plots will be used if there are 10 or more studies investigating the same outcome to assess for asymmetry. If asymmetry is found present in the studies, we will consider rating down the overall certainty of evidence for the outcome.

Data synthesis

We will pool extracted data for meta-analysis using RevMan [16]. For dichotomous variables, we will report pooled risk ratio (RR) along with a 95% confidence interval (CI). For continuous variables, we will report mean differences along with a 95% confidence interval (CI). Meta-analysis will be performed using a random-effects model, unless there is a very small number of studies or significant statistical heterogeneity, in which case we will consider both fixed-effects and random-effects models. We will evaluate statistical heterogeneity using the I-squared statistic, the chi-squared test, and visual inspection of the forest plots. For the purpose of this study, and based on Cochrane Collaboration recommendations, we will consider a I^2 over 80% to indicate substantial heterogeneity; 60 to 80% will indicate moderate heterogeneity and percentages lower than 60% to indicate little to no important heterogeneity [14]. Although categorizing I^2 heterogeneity may not be appropriate and thresholds may be misleading as heterogeneity depends on several factors [17], we will focus on exploring sources of heterogeneity as described in the following section.

Subgroup analysis and investigation of heterogeneity

We will consider a number of subgroup analyses in order to address clinical heterogeneity. These will include surgical ICU patients (including neurosurgery, cardiac surgery, and trauma) versus medical ICU patients, patients receiving early EN versus those receiving late EN, and continuous feeds equal to or lasting more than 18 h compared to those lasting less than 18 h. To address methodological heterogeneity, we will conduct subgroup analyses to compare high risk-of-bias studies versus lower risk-of-bias studies. We plan to use the restricted maximum likelihood (REML) to estimate heterogeneity variance; however, we may consider using an alternative method depending on the size of studies included in the analysis and the frequency of heterogeneity events [18]. In alignment with recent guidelines, early enteral nutrition will be defined as EN started within 48 h of ICU admission, whereas late EN will be defined as EN started greater than 48 h after ICU admission [1]. Surgical patients will be identified per the author's classification. The results of the subgroup analyses will be compared in the summary of findings table. Any subgroups that have a p-value of < 0.05 will be evaluated using ICEMAN for subgroup credibility [19]. We hypothesize that (1) the surgical ICU patients will experience more negative outcomes compared to medical ICU patients, including GI intolerances, potentially due to the effects of anesthesia or surgical procedures; (2) the late EN subgroups will experience more negative outcomes, including GI intolerances, than the early EN subgroup; (3) participants with continuous feeds lasting 18 or more hours will experience more negative outcomes compared to participants with continuous feeds lasting less than 18 h; and (4) there will be more negative outcomes in studies with a lower risk of bias than those with a high risk of bias.

Ethics and dissemination

Ethics board approval is not required as this review is using published data on anonymous participants. We will employ our search criteria and begin selecting studies in the fall of 2022. Data extraction will follow. Once completed, results will be presented at conference proceedings. The final manuscript will be submitted to a peer-reviewed journal for publication.

Discussion

This proposed systematic review aims to determine whether continuous or intermittent enteral feeding is associated with higher rates of diarrhea and other adverse GI outcomes, as well as to determine which feeding modality is associated with better meeting patients' nutritional goals. This review also seeks to determine whether differences exist between relevant subgroups such as early versus late EN and surgical vs. medical ICU patients receiving EN. Strengths of this review include adherence to the PRISMA-P statement, publishing of this protocol a priori, determining the certainty of evidence using GRADE, and use of a trial sequential analysis.

Diarrhea remains a costly and prevalent complication in patients admitted to the ICU and contributes to numerous adverse outcomes including dehydration, hypovolemia, electrolyte imbalances, loss of dignity, and decreased quality of life. In the absence of contraindications, enteral nutrition remains preferred over parenteral nutrition in critically ill patients due to its contribution to maintaining integrity of the GI tract, lower rates of infectious complications, and lower cost. Evidence obtained through completion of this review will be helpful in informing future guidelines regarding choice of feeding modality in ICU patients, as well as to guide selection of feeding modality individual patients. This review will also

serve to identify areas of research opportunity, potentially guiding new studies in this field.

This systematic review and meta-analysis will help inform future trial development regarding the effect of continuous versus intermittent enteral nutrition on incidence of diarrhea in patients admitted to the ICU.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-024-02652-8.

Supplementary Material 1: Supplementary 1. Supplementary data: Search strategy.

Authors' contributions

The protocol was designed by LSA, AMC, and JCD. The first draft was written by LSA and AMC, was subsequently reviewed by JCD, and revised appropriately. The search strategy was developed by KC and reviewed by KD. The manuscript was reviewed and revised for important intellectual content by LM, SO, BR, and JT. All authors approved the final manuscript prior to publication.

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Declarations

Consent for publication

Not required.

Competing interests

The authors declare that they have no competing interests.

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