PEER REVIEW HISTORY

ARTICLE DETAILS

Title (Provisional)

Does Intermittent Nutrition Enterally Normalise hormonal and metabolic responses to feeding in critically ill adults? A protocol for the DINE-Normal proof-of-concept randomised parallel group study

Authors

Beattie, Clodagh; Thomas, Matt; Borislavova, Borislava; Smith, Harry; Ambler, Michael; White, Paul; Hayes, Kati; Milne, Danielle; Ramesh, Aravind; Gonzalez, Javier; Betts, James; Pickering, Anthony

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VERSION 1 - AUTHOR RESPONSE

Dear BMJ Open editorial team,

Many thanks for your consideration of our manuscript. We appreciate the time, expertise and feedback from all reviewers. We have addressed each comment in turn below.

We paid particular attention to: clarifying the methodology for delivery of the diurnal intermittent and continuous feeding regimes; updating the protocol registry; and development of the limitations section in the discussion.

As requested, we have submitted a manuscript copy with tracked changes and a clean copy. Thank you for the reconsideration of our manuscript.

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Dr. Tim Rahmel, Universitätsklinikum Knappschaftskrankenhaus Bochum
Comments to the Author:
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reshaping intensive care practices. Therefore, the study results should be of great interest.

While the protocol is commendably comprehensive, I'd like to highlight some potential areas for improvement, which may help to enhance the robustness of their planned study:

Limitations:
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The primary purpose of this proof-of-concept study was to assess whether we could show evidence of an impact of intermittent feeding on metabolic and hormonal outcome measures. We agree that there is a risk that the effect may not be clearly demonstrated in the critically ill population, but this would also be an important finding. Our power calculation has taken a conservative approach and has 90% power to detect an effect size of 1.26 (compared to the effect size of 2.1 seen in the healthy population). Our study will provide data to inform future studies of this important area. Regarding secondary end points – these include the feasibility of running this study at a larger scale to provide definitive evidence of an impact on patient-centred outcomes. We think we will be able to address this important issue within the scope of the planned study size.

-This is particularly critical given safety concerns based on existing literature regarding feeding intolerance related to intermittent feeding in ICU patients.

As this reviewer has correctly highlighted, safety concerns regarding feeding intolerance remain controversial in the literature and therefore warranted inclusion in our study. With patient safety of paramount importance, we have set out to report on a wide range of pertinent gastrointestinal outcomes in our study. We agree these should be interpreted with caution as the study is not adequately powered for us to draw conclusions to guide clinical practice.

In addition, the selection of peak plasma insulin as the primary endpoint may be also suboptimal, given the high prevalence of insulin resistance among critically ill patients, including those with sepsis. A brief discussion on this matter would be beneficial.

We agree that insulin resistance is an issue seen in this study population. The continuous administration of enteral feed is thought to contribute to this resistance seen in critically ill patients. Our choice of insulin and c-peptide as primary outcome measures is based on the physiological pulsatile endogenous release in response to a meal – rather than the impact of this release on the circulating plasma glucose. While patients may be commenced on insulin infusions the c-peptide assay will give us a measure of the endogenous release from the pancreas seen across the two feeding regimes (as described in p6). As such we think this is appropriate.

Clear delineation of criteria for identifying critically ill patients is lacking, potentially

encompassing elective post-operative/post-interventional cases. These rather constitute a distinct subgroup.

We are not aware of a universally accepted definition of critical illness. We report ICNARC, APACHE II and SOFA score data in baseline demographics, the latter two of which are international recognised metrics of illness severity.
By only including patients who are expected to require enteral nutrition for >48 hours, we exclude most post-operative/post-interventional cases.

We feel that our broad inclusion criteria allow us to reflect the true spectrum of patients who receive enteral feeding in intensive care. Studying the physiological response to intermittent feeding is relevant for all those who are expected to require enteral feeding for >48 hours. Indeed, it may harm the external validity of our study to exclude post-operative/interventional cases.

We agree that the select subgroup of patients having short-term feeding requirements mentioned may behave differently, and that it is important to consider whether some patient groups may have greater/lesser benefit from intermittent feeding regimes. We will consider this suggestion for further work, with a larger patient sample from which to draw meaningful subgroup analyses.

The small sample size of critically ill patients may limit the study's generalizability and obscure relevant subgroup effects.

Given the aforementioned, it's worth considering whether the anticipated beneficial effects apply uniformly across all critically ill patients. Here, if subgroup analysis might reveal particular cohorts likely to benefit more substantially. Identifying such subgroups, if feasible, would be advantageous.

The sample size calculated to meet the aims of this study was drawn from work in healthy volunteers, with adjustments made for the potentially smaller effect size in a critically ill population. We agree that further work on a larger sample size will be necessary to study subgroup effects and draw conclusions which can be generalised to clinical practice. Indeed, as stated in our discussion, we plan to conduct a larger study with these aims in mind.

- The methodology for determining individual calorie targets on day 2 warrants clarification.

The methodology is stated in the nutrition guideline provided as an appendix to the protocol in the supplementary material. Patient requirements are determined by specialist dietitians using predictive equations. On study day 2 the aim is to provide up to 60% of energy requirements if obese and up to 80% if not with 0.2-0.32g/kg of nitrogen per day.

- Information regarding the specific tube feeding utilized was not found in the protocol.

We specified 'The feed type will be Nutrison Protein Plus (Nutricia, UK' in the protocol (Trial Intervention).

Reviewer: 2
Dr. Jean-Christophe Callahan, Centre Hospitalier du Mans
Comments to the Author:
I would like to thank the editors of BMJ open for the opportunity to review this paper. I also commend the authors of this protocol for conducting a study which could impact the management of crucial care patients worldwide.
I have a few questions or comments regarding this manuscript.
Abstract
Introduction
Page 3, lines 10,11: “Over half of patients who spend >48 hours in the intensive care unit (ICU) are fed via a nasogastric (NG) tube.”
With the risk of being seen as overly pedantic, I would suggest replacing “nasogastric” simply with “gastric” as feeding tubes are also routinely put via the orogastric route.

Updated in manuscript

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Updated in manuscript to “Here we present the protocol for a proof-of-concept study investigating the effects of diurnal intermittent versus continuous feeding on hormonal and metabolic outcomes for patients in the intensive care unit.” (page 2)

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Although this is true, for the sake of clarity I do not think that these two terms should be used interchangeably in the manuscript. The review by Satomi Ichimaru published in NCP in 2018 gives a clear and useful basis for the definitions of the

different enteral feeding modalities (PMID: 29924423). On this basis I would suggest replacing “bolus” by “intermittent” when describing the intervention.

Updated in manuscript

Page 6, lines 55-60 and page 7, lines 3,4: “Optimising the delivery of nutrition to critically ill patients has the potential to provide several benefits: improved metabolic function with maintained insulin sensitivity; reduced catabolism and sarcopenia, which would hasten rehabilitation and improve long-term functional status; altered immune response to improve outcomes in sepsis and better entrainment of circadian rhythms with improved sleep/wake cycles, potentially resulting in reduced delirium and less risk of post-traumatic stress disorder.”
The provided reference by Gonzalez and al. is not sufficient for all the statements made in this sentence.

Updated in manuscript with references to address all statements

As the planned intervention is the association of two separate interventions (i.e. intermittent feeding and nocturnal fasting) as compared to the control (continuous feeding) group, I would suggest, for clarity, even more clearly separating the expected benefits of each.
For example, page 6, lines 54,55: “All of these plausible beneficial effects of intermittent feeding may improve tolerance to and recovery from critical illness.” Some of the described beneficial effects, for example those attributed to diurnal feeding, could be inhibited by an intermittent feeding pattern spread over the 24-hour period. For this reason, also, I would suggest using “diurnal intermittent” in the place of “intermittent”, when describing the intervention. For example, page 7, lines 13,14: “The DINE-N study aims to provide evidence to assess whether intermittent rather than continuous feed is advantageous.”

We value this insight from the reviewer and agree that our intervention may offer plausible benefits from diurnal intermittent feeding and nocturnal fasting and have tried to make this clearer in the manuscript. Nevertheless, the pattern as a whole mimics a typical human eating pattern and we believe should be seen as a package because we are uncertain of the relative importance of each component.

Amendment made to the sentence in the introduction (page 5). We have now acknowledged this point in the discussion amongst limitations of the study (page 17).

Amendments made throughout manuscript to reflect “diurnal intermittent” in place of “intermittent”

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Page 7, line 33: I would suggest replacing “improvement” by “response”.

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How is this risk defined? Is a specific score used or is it left to the investigator's discretion?

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Trail intervention and comparator
When reading these chapters, I understand that the intervention and comparator groups differ according to three parameters: intermittent feeding, nocturnal fasting and caloric intake. If this is not the case, please clarify. Would it be possible to specify the expected caloric intake in the two groups during day 1 and day 2 (in kcal/kg)? Furthermore, the use of two different feed types with two different compositions and calories per mL is a risk of bias.

It is not the case that the groups are planned to differ by caloric intake or feed used and with the randomised design we anticipate balance between the groups in these and other characteristics. The only difference is the pattern of feed delivery.

The local guidelines for provision of nutrition and the datasheets for the feed used are given in the supplementary material and are used by specialist intensive care dieticians. The provision of 600ml of the usual feed (see supplementary material) will provide 750kcal in 24 hours (study day 1). We do not yet know the average weight of the participants in the study.

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Discussion
As discussed above, there, is in my view, a risk of bias due to the fact that there are three fundamental differences between the intervention and control group (intermittent feeding, nocturnal fasting and caloric intake). If the study does show a difference in the outcomes between the two groups it might be difficult to ascertain

which of these factors is responsible. Maybe this could be discussed in the paragraph pertaining to the limitations of the study (page 17, line 57)?

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Competing interests of Reviewer: None

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Competing interests of Reviewer: I have no competing interests.

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