Effects of standard versus energy-dense formulae on gastric retention, caloric delivery, and glycaemia in critically ill patients

Authors

Lee-anne S Chapple[1,2,3] (PhD)

Matthew J Summers[1,2] (MDiet)

Luke M Weinel[1] (BSc (Hons))

Yasmine Ali Abdelhamid[2,5] (MBBS)

Palash Kar[1,2] (PhD)

Seva Hatzinikolas[3] (DipAppSc (NucMed))

Deborah Calnan[4] (BMedRad (NucMed))

Madison Bills[4] (BMedRadSc (NucMed) (Hons))

Kylie Lange[3] (BSci (Hons))

Alexis Poole[1,2] (BNSc (Hons))

Stephanie N O'Connor[1,2] (MNSc)

Michael Horowitz[3] (PhD)

Karen L Jones[3] (PhD)

Adam M Deane[5] (PhD)

Marianne J Chapman[1,2,3] (PhD)

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jpen.2065.

Affiliations

[1]Intensive Care Unit, Royal Adelaide Hospital, Adelaide, South Australia, Australia

[2]Discipline of Acute Care Medicine, The University of Adelaide, Adelaide, South Australia, Australia

[3]Centre of Research Excellence in Translating Nutritional Science to Good Health, The University of Adelaide, Adelaide, Australia

[4]Department of Nuclear Medicine, PET and Bone Densitometry, Royal Adelaide Hospital, Adelaide, South Australia, Australia

[5]The University of Melbourne, Melbourne Medical School, Department of Medicine and Radiology, Royal Melbourne Hospital, Parkville, Australia

Corresponding author

Lee-anne Chapple

Mailing address: 4G751, ICU Research, Royal Adelaide Hospital, Port Road, Adelaide, South Australia 5000, Australia

Email: lee-anne.chapple@adelaide.edu.au

Phone: +61 8 7074 1763

Conflict of interest

None declared

Financial disclosure

This study was supported by an American Society of Parenteral and Enteral Nutrition Research Grant. The Royal Adelaide Hospital provided infrastructure and administrative support.

Clinical relevancy statement

Management of enteral feeding intolerance often includes the substitution of a standard (1 kcal/ml) enteral formula with an energy-dense formula. Using high quality methodology, this study shows that there is more gastric retention of an energy-dense compared to a standard formula. The use of an energy-dense formula does not improve caloric delivery to the small intestine in critically ill adults.

Word count: 4797

Abstract

Background

Energy-dense formulae are often provided to critically ill patients with enteral feed intolerance with the aim of increasing calorie delivery, yet the effect on gastric emptying is unknown. The rate of gastric emptying of a standard compared to an energy-dense formula was quantified in critically ill patients.

Methods

Mechanically ventilated adults were randomized to receive radiolabelled intragastric infusions of 200ml standard (1kcal/ml) or 100ml energy-dense (2kcal/ml) enteral formulae on consecutive days in this non-inferiority, blinded, cross-over trial. The primary outcome was scintigraphic measurement of gastric retention (% at 120min). Other measures included: area under the curve (AUC) for gastric retention and intestinal calorie delivery (calculated from gastric retention of formulae over time), blood glucose (peak and AUC), and intestinal glucose absorption (using 3-O-methylglucose (3-OMG) concentrations). Comparisons were undertaken using paired mixed-effects models. Data presented are mean ± standard error.

Results

Eighteen patients were studied (M:F 14:4; age 55.2±5.3 years). Gastric retention at 120min was greater with the energy-dense formula (standard: 17.0±5.9 vs energy-dense: 32.5±7.1; difference 12.7 (90% CI 0.8–30.1) %). Caloric delivery (AUC_{120}: 13038±1119 vs 9763±1346 kcal/120min; P=0.057), glucose control (peak glucose 10.1±0.3 vs 9.7±0.3 mmol/L; P=0.362, and glucose AUC_{120} 8.7±0.3 vs 8.5±0.3 mmol/L.120min; P=0.661) and absorption (3-OMG $AUC_{120:}$ 38.5±4.0 vs 35.7±4.0 mmol/L.120min; P=0.508) were not improved with the energy-dense formula.

Conclusion

In critical illness, administration of an energy-dense formula does not reduce gastric retention, increase calorie delivery to the small intestine, nor improve glucose absorption or glucose control; instead there is a signal for delayed gastric emptying.

Introduction

During mechanical ventilation, critically ill patients usually receive enteral nutrition (EN) delivered gastrically[1,2]; however, delivery is often inadequate with observational studies reporting patients receive 50-60% of estimated calorie targets[3,4]. Inadequate nutrient delivery is primarily due to delayed gastric emptying, which occurs in up to 50% of mechanically ventilated patients[5]. In clinical practice, delayed gastric emptying is usually identified by clinical symptoms including regurgitation, vomiting and abdominal distention, or through aspirating the nasogastric tube and establishing a 'large' (i.e. ≥ 250-500 ml) volume retained in the stomach, which is termed 'enteral feed intolerance'[6].

Strategies to manage enteral feed intolerance secondary to delayed gastric emptying include administration of prokinetic medications, post-pyloric feeding, or supplemental parenteral nutrition[7,8]; however, these are associated with increased costs, workload, or potential negative side effects. Another common strategy is to replace a standard enteral formulae (~1 kcal/ml)[9] with more energy-dense formulae (i.e. ~2 kcal/ml), with the intent of reducing the volume infused into the stomach[10]. Despite the fact that energy-dense formulae are widely used it has never been established that their use results in improved caloric delivery to the small intestine and increased nutrient absorption[11].

In health, gastric emptying of low nutrient liquid follows a volume-dependent process. As nutrient content increases, emptying assumes a linear pattern so that small intestinal delivery approximates 1-4 kcal/min as a result of inhibitory feedback triggered by the interaction of nutrients with the small

intestine[12]. This caloric emptying is slowed in critical illness, probably primarily as a result of up-regulation of normal small intestinal feedback mechanisms, including increased levels of the gut hormones cholecystokinin (CCK), peptide YY (PYY), and glucagon-like peptide-1 (GLP-1)[13-16]. While caloric content is the primary driver of gastric emptying, other factors may play a role including macronutrient composition or volume. To account for the greater caloric content, energy-dense formulae typically have an increased lipid profile compared to a standard formula. In health, an increasing fat percentage is associated with a greater slowing of gastric emptying[17,18], due to an increase in CCK and PYY secretion[19]. While in patients with chronic obstructive pulmonary disease (COPD), gastric emptying has been shown to be demonstrably slower after a 'high' fat meal[20].

We have previously published a post-hoc analysis of two different cohorts of critically ill patients that had gastric emptying studies conducted with an isovolumetric bolus 'test meal' of either a 1 or 2 kcal/ml formula[21], which showed greater retention of energy-dense formula in the stomach after four hours, consistent with slower gastric emptying. Accordingly, it is physiologically plausible that the prescription of energy-dense formulae may further retard the rate of gastric emptying and, hence, reduce nutrient delivery and absorption in critically ill patients. Due to methodological limitations of the published post-hoc analysis, this signal requires evaluation using more robust methodology. The aim of this study was to evaluate the effect of caloric density on gastric emptying measured using the 'gold standard' technique and methodology of scintigraphy in critically ill patients in a randomized, blinded, cross-over, non-inferiority trial design. The secondary aims were to measure glycemic control and intestinal glucose absorption in response to standard versus energy-dense formulae.

Methods

A randomized, double-blind, cross-over, non-inferiority study was performed on consecutive days in critically ill patients. Patients admitted to the Royal Adelaide Hospital (RAH) Intensive Care Unit (ICU) from February 2017 to February 2019 were screened for eligibility and written, informed consent obtained from the next of kin. The study was approved by the Central Adelaide Local Health Network Human Research Ethics Committee (HREC/16/RAH/503) and was performed according to the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research.

Participants

Inclusion criteria included: (1) mechanically ventilated patients anticipated to remain ventilated for a further ≥48 hours; (2) aged ≥18 years of age; and (3) receiving or planned to receive EN via a nasogastric tube. Patients were excluded if they met one of the following criteria: (1) pregnant; (2) receiving drugs known to affect gastric function (**Supplemental File 1**); (3) upper gastrointestinal surgery during or prior to their admission (oesophageal, stomach or duodenal); and (4) unable to obtain informed consent. Study conduct required availability of research staff and the gamma camera and hence screening was only conducted if the study logistics could be completed. Enteral formula intolerant patients (defined as GRV ≥250 ml as per clinical practice in the participating site) remained eligible provided they had not received gastrokinetic drugs in the preceding 24 hours.

Protocol

Patients were studied on consecutive days, where they received standard (1 kcal/ml) formulae on one day and energy-dense (2 kcal/ml) formulae on the other day. A randomization schedule for order of EN formulae delivery was developed by a research nurse who was not involved in patient recruitment, data collection, or data analysis using random.org.au online random number generator. The schedule was saved as a password protected file on the shared hospital server. Research nurses prepared and delivered the 'test meals' in the absence of other research staff to ensure those conducting the measurements remained blinded to the intervention.

The protocol is summarized in **Figure 1**. Following a four hour fast, the nasogastric tube was aspirated, and contents of the stomach discarded, prior to the commencement of the study. At t = -5, an intragastric 'test meal' was infused by the research nurse over 5 minutes. The 'test meal' contained 200 ml of standard formula (Nutrison® 1kcal/ml, Nutricia Australia, containing carbohydrate 49%, fat 35%, and protein 16%, osmolality 305 mOsm/kg H_2O) or 100 ml of energy-dense formula (TwoCal® 2kcal/ml, Abbott Nutrition, containing carbohydrate 43%, fat 40%, and protein 17%, osmolality 690 mOsm/kg H_2O), combined with 3 g of 3-O-Methyl-D-gluco-pyranose (3-OMG) (Sigma-Aldrich, NSW, Australia) dissolved in 5 ml H_2O and 20 MBq ^{99m}Tc-calcium phytate colloid[22]. 'Test meals' with identical calorie contents but differing volumes were chosen to replicate clinical utilization of energy-dense formulae. Following the four-hour study period, EN was re-commenced. Blood samples were analyzed at the bedside for blood glucose concentrations using a portable glucometer and blood glucose concentrations treated according to the local hospital protocol (i.e. blood glucose target <10 mmol/l).

Measurements

Scintigraphic images for the measurement of gastric emptying were acquired at 1-minute intervals for 60 minutes and 3-minute intervals thereafter, for a total of four hours using a mobile gamma camera

(DigiRad 2020tc, Gammasonics, NSW, Australia) angled at left anterior oblique (LAO) 45° with the patient lying in the semi-recumbent position[23]. Regions-of-interest were drawn around the total stomach by an experienced nuclear medicine technician not involved in any other aspect of study conduct. Data were corrected for radionuclide decay and gastric emptying curves (expressed as % of the maximum content of the total stomach i.e. 100% at t=0) were derived. The content of the total stomach following the 'test meal' was then calculated at 15, 30, 45, 60, 90, 120, 150, 180, 210 and 240 minutes. Gastric emptying scintigraphic data were analyzed by the same individual (SH) and checked by a second investigator (KLJ), both trained in nuclear medicine and blinded to the study conditions.

Arterial blood samples were obtained prior to the 'test meal' infusion (t=-5 mins) and at regular time intervals (t=15, 30, 45, 60, 90, 120, 150, 180, 210 and 240 min) with plasma collected into chilled ethylenediaminetetraacetic acid (EDTA) tubes and serum samples collected into z serum tubes and kept on ice until centrifugation. Plasma/serum were separated by centrifugation (3200 RPM for 15 min at 4°C) and the resulting plasma/serum stored at -70º C for subsequent analysis. Glucose absorption was assessed using serum concentrations of the non-absorbable glucose analogue 3-OMG (Sigma-Aldrich, NSW, Australia), an inert sugar that is not metabolized by the liver and is renally cleared[24]. To allow for paired data analysis, serum 3-OMG concentrations were analyzed for patients with samples available on both study days using High Performance Liquid Chromatography. The rate of glucose absorption is indicated by the area under the 3-OMG concentration curve and peak concentration[23].

Baseline demographic and patient clinical characteristics were also collected including age, sex, admission diagnosis, Acute Physiology and Chronic Health Evaluation (APACHE) II score on ICU admission and study day 1, ICU length of stay, need for dialysis, and Risk, Injury, Failure, Loss of

kidney function, End-stage kidney disease (RIFLE) classification. Data were also collected during the study periods including nutrition support received, gastrointestinal intolerance, and insulin, vasopressor, opiates, and inotrope administration.

Outcomes

Primary

To compare the rate of gastric emptying of 200 ml of standard and 100ml of energy-dense liquid formula in critically ill patients; with gastric emptying assessed as percentage gastric retention at 120 mins using scintigraphy.

Secondary

To evaluate the effects of standard and energy-dense formulae on:

- Caloric delivery to the small intestine (percentage of 'test meal' emptied from stomach /100 * kcal in 'test meal')
- Intestinal glucose absorption measured using AUC serum 3-OMG concentrations
- Blood glucose concentrations (peak and AUC)

Sample size calculation

Data on gastric emptying from a previous scintigraphic study in the critically ill estimated the within subject variability of gastric retention to be 42%[21]. Based on this, n=20 patients provided 80% power at 5% significance to determine non-inferiority of gastric retention with a non-inferiority margin of 24 percentage points. Non-inferiority was indicated if the upper bound of the 90% confidence interval of the difference in gastric retention was less than the non-inferiority margin. That is, gastric retention at t=120 minutes for the energy-dense formula will be no more than 24 percentage points more than for the standard formula. The non-inferiority margin was based on both expert opinion and previous research[21].

Statistical analyses

Total areas under the curve (AUC) from baseline to 15, 60, 120, 180 and 240 minutes were calculated for gastric emptying, calorie delivery and blood glucose using the trapezoidal rule. Blood glucose AUCs were scaled for study duration and blood glucose peak and AUCs adjusted for differences in baseline levels. Data are presented as mean ± standard error of the mean (SEM).

The primary outcome is presented as a 90% confidence interval (CI) for assessment of non-inferiority[25]. All secondary outcomes were analyzed with a mixed effects model with fixed effects for treatment (standard or energy-dense formulae) and visit order (first or second), and a random subject intercept to account for the repeated visits per subject. Mean differences between groups are presented with 95% CI. P-values of <0.05 were considered significant. No adjustments for multiple testing were made.

Recruitment stopped early for this trial due to lower than anticipated recruitment rates, with challenges in completing consecutive study days. In addition, paired data were not available in all participants due to technical difficulties with the gamma camera.

Results

Consent was obtained for 24 patients, with 18 patients studied on at least one study day. Reasons for exclusion and incomplete studies are shown in **Figure 1**. Patients contributing at least one study day were primarily male (78%), aged 55.2 ± 5.3 years, with primary admission diagnoses of neurological and cardiac (**Table 1**). Patients were studied 6.7 ± 1.2 days after ICU admission. Data on medications and nutrition received in the 24 hours prior to study day 1, and on the study days are included in **Supplemental Table S1**. All patients were tolerating enteral feeding (GRV<250ml) the day prior to study day one.

Gastric emptying

Fifteen patients had gastric emptying data for the standard formula and 10 patients had gastric emptying data for the energy-dense formula (Figure 1 and **Table 2**). Of these, 10 patients had gastric emptying data available on both study days.

For the primary outcome, the 90% CI for the difference in gastric retention (%) at 120 mins crossed the pre-defined non-inferiority margin (standard: 17.0 ± 5.9 vs energy-dense 32.5 ± 7.1 %; mean difference 12.7 (90% CI 0.8 – 30.1) %; P=0.085 (Table 2; **Figure 2**).

There was no difference in gastric retention, when measured using AUC 0-120 mins (AUC_{120} standard: 5481 ± 559 vs energy-dense: 7118 ± 673 %.120min; difference 1638 (95% CI -58 – 3333) %.120min; P=0.057) (Table 2). AUCs at 15, 60, and 240 min were also similar between formulae (Table 2).

Mean intestinal calorie delivery was not statistically different between the two formulae (AUC_{120}: standard: 13038 ± 1119 vs energy-dense: 9763 ± 1346 kcal.120min; difference -3275 (95% CI -6666 – 116) kcal.120min; P=0.057) (Table 2; **Figure 3a**) (see also AUC_{15}, AUC_{180} and AUC_{240}; Table 2).

Intestinal caloric delivery per minute (kcal/min) (i.e. the amount of calories per unit time emptying from the stomach) over the first 120 mins was not different between the two formulae: (AUC_{120}: 235 ± 24 vs 162 ± 29 kcal/min.120min; difference -73 (-157 – 11) kcal/min.120min; P=0.078 (Table 2, **Figure 3b**).

Glucose absorption

3-OMG concentrations (glucose absorption) were analyzed from samples obtained in patients (n=14) with paired samples, i.e. both study days, and were similar with the two formulae at all timepoints (all P>0.3) (Table 2; **Figure 4**).

Blood glucose concentrations

The mean baseline blood glucose was similar between the two formulae (7.1 ± 0.4 vs 6.7 ± 0.5, difference -0.4 (95% CI -1.6 – 0.7) mmol/L; P=0.435). After adjusting for differences in baseline blood glucose, there were no differences in peak blood glucose (10.1± 0.3 vs 9.7 ± 0.3 mmol/L; difference -0.4 (95% CI -1.3 – 0.5) mmol/L; P=0.364**)** nor glucose AUC_{120} (8.7 ± 0.3 vs 8.5 ± 0.3 mmol/L; difference -0.2 (-0.9 – 0.6) mmol/L; P=0.661) (see also glucose AUC_{60} and AUC_{240}) (Table 2; **Figure 5**).

Discussion

The primary outcome of this trial is that 120 minutes after gastric nutrient delivery there was 12.7 % less content retained in the stomach using standard formulae when compared to the energy-dense formula i.e. the rate of gastric emptying of the standard formula was faster. These data establish that the delivery of the same amount of calories in a smaller volume using an energy-dense formula into the stomach does not result in faster emptying of nutrients into the small intestine. Rather, it appears that gastric emptying may be unaffected or slowed.

This supports the results of an unpaired retrospective study by our group comparing 18 patients receiving 2 kcal/ml with 22 patients receiving 1 kcal/ml enteral formulae; in the retrospective study, gastric retention AUC at 240 mins was significantly greater (i.e. emptying was slower) in patients receiving energy-dense formula[21]. Combined, these results suggest that the clinical practice of providing energy-dense enteral formulae instead of a standard formula will not improve caloric delivery, with the energy-dense formula providing no significant benefit on gastric emptying, and potentially exacerbating delayed gastric emptying, compared to standard care. This is also supported by results of the TARGET trial, which randomized 4000 mechanically ventilated critically ill adults to receive standard versus energy-dense (1.5 kcal/ml) formulae, delivered at the same rate, and reported larger gastric residual volumes and greater use of prokinetics in patients receiving the energy-dense formula[26]. Therefore, the substitution of a standard with an energy-dense enteral formula for the sole reason of delayed gastric emptying should not be advocated in clinical practice.

A number of individual factors, either in isolation or cumulatively, may be responsible for the trend towards faster gastric emptying of the standard enteral formula. In order to afford a greater energy-density, the 2 kcal/ml bolus had a higher fat content (7.8 vs 8.9 g fat), and fat has been shown to slow gastric emptying in health[18], type 2 diabetes[27], and patients with COPD[20]. Furthermore, while the protein contents of the formulae were similar (8.0 vs 8.4 g protein) the type of protein differed, with the 1 kcal/ml primarily whey-based and the 2 kcal/ml primarily constituting casein. In 21 healthy volunteers, a cross-over trial compared rates of gastric emptying of isocaloric, isovolumetric enteral formulae with non-coagulating (predominantly whey) and casein protein, demonstrating that the non-coagulating formula emptied faster[28], which may suggest that protein type is a stronger determinant of gastric emptying than the total protein content. The two formulae in our study also differed in osmolality, with the energy-dense formula having a higher osmolality (305 vs 690 mOsm/kg H_2O), and lower osmolality may increase the rate of gastric emptying. In order to maintain isocaloric boluses, the volume of formula instilled was greater on the standard formula study day. Volume has been shown to be a driver of gastric emptying under isocaloric conditions[29] through activation/stimulation of stretch receptors which in-turn influences intragastric pressure and gastric emptying[30], yet this reflects usual clinical practice (i.e. reduced volume whilst maintaining calories). In addition, this study assessed the physiological response to a single bolus of enteral formulae; however, critically ill patients are generally fed continuously (i.e. 24 hours). A recent trial in 63 critically ill patients compared isocaloric intermittent to continuous feeding and reported no differences in rates of diarrhoea or vomiting, use of prokinetics, or number of days with gastric residual volumes >300 mL[31]; therefore, it could be considered that the rates of gastric emptying shown with bolus delivery in our study are likely to be similar with continuous infusion of nutrients, but this requires confirmation.

While there was a signal of more rapid gastric emptying and delivery of nutrient to the intestine with the standard enteral formula, the 3-OMG results show similar rates of glucose uptake into the plasma between the two formulae. Glucose (3-OMG) absorption is related to gastric emptying, yet direct factors within the small intestine that are influenced by critical illness may also affect glucose absorption[23,32]. Another explanation for the lack of signal in intestinal glucose uptake may be that we only included patients with paired data for 3-OMG analyses, and hence the patient population differs between those with scintigraphic and blood glucose data. Further, glucose control did not differ between the two groups after adjusting for differences in baseline blood glucose levels. Kar, *et al.* reported a non-significant increase in blood glucose following a isovolumetric bolus of standard formula when compared to an energy-dense formula[21]. The discrepancies in these results may be due to the different bolus volumes between these two studies.

In this study a cross-over study design was used in which patients received both treatments separated by <24 hours. This allowed for control of factors known to potentially affect gastric emptying including age, sex, hormonal changes and timepoint after ICU admission. Consistent patient posture between the two study days was confirmed, and patients on medications known to influence gastric emptying were excluded. High-quality methodologies including scintigraphy for measurement of gastric emptying and 3-OMG for measurement of glucose absorption were used. The major limitation of this study is one that is common in nutrition research, being the inability to manipulate one factor (such as calories) without affecting another (such as fat content), which precludes the ability to separate individual nutrient effects on the defined outcomes. It may be that the different protein type (casein versus whey), osmolality, fat content, or volume in these two formulae were responsible for the different results found in this trial; these factors may not differ for all commercially available formulae. Similarly, this study assessed the physiological response to a

single bolus of enteral formulae rather than continuous feeding more frequently used in clinical practice. However, the macronutrient profiles of the two formulae were controlled, which is a true reflection of clinical practice, and the same methodology used on each study day, hence, the results of this study remain applicable. Recruitment for this trial was challenging and limited by the number of eligible patients who remained mechanically ventilated for sufficient periods to enable the cross-over study design and were able to participate in the 4-hour scintigraphic measurements on days when research equipment and staff were present. For this reason, screening was only conducted on days where study logistics (adequate staff and research equipment) allowed the study to proceed, and hence a comprehensive CONSORT diagram was not included. The study was continued for two years before termination but the number of study participants with scintigraphic data on both study days was still less than the sample size of 20; therefore, the study was underpowered based on the predefined non-inferiority margin. While greater power may result in the non-inferiority margin not being breached, there is almost absolute confidence that the energy-dense formula would not empty faster than the standard formula, even with more patients included. All patients included in this study were also tolerating enteral feeding according to gastric residual volumes the day before study day one and; therefore, it is unknown how these different enteral formulae might be handled by critically ill patients with feed intolerance.

Conclusion

In critically ill adults, the use of energy-dense formulae does not increase the rate of emptying from the stomach, increase caloric delivery to the small intestine or improve glucose absorption or control. Accordingly, there appears to be no physiological or nutritional basis to support the prescription of energy-dense enteral formula on the sole premise of improving energy delivery.

References

1. Casaer MP, Van den Berghe G. Nutrition in the acute phase of critical illness. *NEJM.* 2014;370(13):1227-36.
2. McClave SA, Martindale RG, Rice TW, Heyland DK. Feeding the critically ill patient. *CCM.* 2014;42(12):2600-10.
3. Cahill NE, Dhaliwal R, Day AG, Jiang X, Heyland DK. Nutrition therapy in the critical care setting: What is "best achievable" practice? An international multicenter observational study. *CCM.* 2010;38(2):395-401.
4. De Beaux I, Chapman M, Fraser R*, et al.* Enteral nutrition in the critically ill: A prospective survey in an australian intensive care unit. *Anaes Intensive Care.* 2001;29:619-22.
5. Chapman MJ, Nguyen NQ, Deane AM. Gastrointestinal dysmotility: Clinical consequences and management of the critically ill patient. *Gastro Clinics North America.* 2011;40(4):725-39.
6. Blaser AR, Starkopf J, Kirsimagi U, Deane AM. Definition, prevalence, and outcome of feeding intolerance in intensive care: A systematic review and meta-analysis. *Acta Anaesthesiologica Scandinavica.* 2014;58(8):914-22.
7. Singer P, Blaser AR, Berger MM*, et al.* ESPEN guideline on clinical nutrition in the intensive care unit. *Clin Nutr.* 2019;38(1):48-79.
8. McClave SA, Taylor BE, Martindale RG*, et al.* Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN.* 2016;40(2):159-211.
9. Kim H, Stotts NA, Froelicher ES, Engler MM, Porter C. Why patients in critical care do not receive adequate enteral nutrition? A review of the literature. *J Crit Care.* 2012;27(6):702-13.

10. Peake SL, Chapman MJ, Davies AR*, et al.* Enteral nutrition in Australian and New Zealand intensive care units: A point-prevalence study of prescription practices. *Crit Care Resusc.* 2012;14(2):148-53.

11. Bryk J, Zenati M, Forsythe R, Peitzman A, Ochoa JB. Effect of calorically dense enteral nutrition formulas on outcome in critically ill trauma and surgical patients. *JPEN.* 2008;32(1):6-11.

12. Lin HC, Doty JE, Reedy TJ, Meyer JH. Inhibition of gastric emptying by glucose depends on length of intestine exposed to nutrient. *Am J Physiol.* 1989;256(2 Pt 1):G404-11.

13. Chapman M, Fraser R, Vozzo R*, et al.* Antro-pyloro-duodenal motor responses to gastric and duodenal nutrient in critically ill patients. *Gut.* 2005;54(10):1384-90.

14. Nematy M, O'Flynn JE, Wandrag L*, et al.* Changes in appetite related gut hormones in intensive care unit patients: A pilot cohort study. *Crit Care.* 2006;10(1):R10.

15. Nguyen NQ, Fraser RJ, Chapman MJ*, et al.* Feed intolerance in critical illness is associated with increased basal and nutrient-stimulated plasma cholecystokinin concentrations. *CCM.* 2007;35(1):82-8.

16. Summers MJ, Di Bartolomeo AE, Zaknic AV*, et al.* Endogenous amylin and glucagon-like peptide-1 concentrations are not associated with gastric emptying in critical illness. *Acta Anaesthesiologica Scandinavica.* 2014;58(2):235-42.

17. Sachdeva P, Kantor S, Knight LC, Maurer AH, Fisher RS, Parkman HP. Use of a high caloric liquid meal as an alternative to a solid meal for gastric emptying scintigraphy. *Digestive Diseases Sci.* 2013;58(7):2001-6.

18. Clegg M, Shafat A. Energy and macronutrient composition of breakfast affect gastric emptying of lunch and subsequent food intake, satiety and satiation. *Appetite.* 2010;54(3):517-23.

19. Maljaars PW, van der Wal RJ, Wiersma T, Peters HP, Haddeman E, Masclee AA. The effect of lipid droplet size on satiety and peptide secretion is intestinal site-specific. *Clin Nutr.* 2012;31(4):535-42.

20. Akrabawi SS, Mobarhan S, Stoltz RR, Ferguson PW. Gastric emptying, pulmonary function, gas exchange, and respiratory quotient after feeding a moderate versus high fat enteral formula meal in chronic obstructive pulmonary disease patients. *Nutrition.* 1996;12(4):260-5.

21. Kar P, Plummer MP, Chapman MJ*, et al.* Energy-dense formulae may slow gastric emptying in the critically ill. *JPEN.* 2016;40(7):1050-6.

22. Kar P, Cousins CE, Annink CE*, et al.* Effects of glucose-dependent insulinotropic polypeptide on gastric emptying, glycaemia and insulinaemia during critical illness: A prospective, double blind, randomised, crossover study. *Crit Care.* 2015;19:20.

23. Chapman RJ, Templeton M, Ashworth S, Broomhead R, McLean A, Brett SJ. Long-term survival of chronic dialysis patients following survival from an episode of multiple-organ failure. *Crit Care.* 2009;13(3):R65.

24. Fordtran JS, Clodi PH, Soergel KH, Ingelfinger FJ. Sugar absorption tests, with special reference to 3-0-methyl-d-glucose and d-xylose. *Ann Intern Med.* 1962;57:883-91.

25. Flight L, Julious SA. Practical guide to sample size calculations: Non-inferiority and equivalence trials. *Pharm Stat.* 2016;15(1):80-9.

26. TARGET Investigators for the ANZICS Clinical Trials Group, Chapman M, Peake SL*, et al.* Energy-dense versus routine enteral nutrition in the critically ill. *NEJM.* 2018;379(19):1823-34.

27. Gentilcore D, Chaikomin R, Jones KL*, et al.* Effects of fat on gastric emptying of and the glycemic, insulin, and incretin responses to a carbohydrate meal in Type 2 Diabetes. *J Clin Endocrinol Metab.* 2006;91(6):2062-7.

28. Kuyumcu S, Menne D, Curcic J*, et al.* Noncoagulating enteral formula can empty faster from the stomach: A double-blind, randomized crossover trial using magnetic resonance imaging. *JPEN.* 2015;39(5):544-51.

29. Okabe T, Terashima H, Sakamoto A. What is the manner of gastric emptying after ingestion of liquids with differences in the volume under uniform glucose-based energy content? *Clin Nutr.* 2017;36(5):1283-7.

30. Phillips RJ, Powley TL. Tension and stretch receptors in gastrointestinal smooth muscle: Re-evaluating vagal mechanoreceptor electrophysiology. *Brain Res Brain Res Rev.* 2000;34(1-2):1-26.

31. McNelly AS, Bear DE, Connolly BA*, et al.* Effect of intermittent or continuous feed on muscle wasting in critical illness: A phase 2 clinical trial. *Chest.* 2020;158(1):183-94.

32. Deane AM, Rayner CK, Keeshan A*, et al.* The effects of critical illness on intestinal glucose sensing, transporters, and absorption. *CCM.* 2014;42(1):57-65.

Table 1: Demographics and baseline clinical characteristics

	Mean ± SEM n=18
Age, y	55.2 ± 5.3
Male:Female (% male)	14:4 (78)
Weight, kg	91.3 ± 4.3
Body Mass Index, kg/m^2	30.5 ± 1.7
APACHE II at admission	20.8 ± 2.2
APACHE II on study day 1	16.9 ± 1.2
Length of ICU stay, days	15.2 ± 3.5
Days in ICU prior to study day 1	6.7 ± 1.2
Tolerating feeds in 24h prior to study day 1[a] Yes:No, n	 18:0
Diagnostic category, n Trauma Neurology Respiratory Cardiovascular	 4 7 1 6
Dialysis on study day 1, n (%)	4 (22)
RIFLE criteria on study day 1, number No AKI Risk Failure End-stage Kidney Disease	 13 1 3 1
Creatinine on day 1, umol/L	86.1 ± 9.3
Patients with pre-existing diabetes, n (%) HbA1c of diabetic patients (%)	4 (22) 7.4 ± 1.0

AKI: Acute Kidney Injury; APACHE: Acute Physiology and Chronic Health Evaluation; ICU: Intensive Care Unit; RIFLE: Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease; SEM: Standard Error of the Mean.

[a]Aspirate of gastric contents were obtained clinically every 6 hours and "feed intolerance" was defined when one gastric residual volume aspirate was ≥ 250 ml. All other patients receiving feeds were considered to be tolerating feeds.

Table 2: Gastric emptying, blood glucose concentrations, and glucose absorption outcomes between standard and energy-dense formulae

	Standard formula		Energy-dense formula		Difference (90% CI)	P value
	No. patients	Mean ± SEM	No. patients	Mean ± SEM		
Gastric retention						
Primary outcome: Gastric retention at 120 min (%)	15	17.0 ± 5.9	10	32.5 ± 7.1	12.7 (0.8 – 30.1)	0.085
	Standard formula		Energy-dense formula		Difference (95% CI)	P value
	No. patients	Mean ± SEM	No. patients	Mean ± SEM		
Gastric retention AUC						
Gastric retention AUC_{15} (%.15min)	15	1320 ± 31	10	1416 ± 38	96 (-63 – 198)	0.064
Gastric retention AUC_{60} (%.60min)	15	3862 ± 251	10	4617 ± 305	755 (-250 – 1760)	0.106
Gastric retention AUC_{120} (%.120min)	15	5481 ± 559	10	7118 ± 673	1638 (-58 – 3333)	0.057
Gastric retention AUC_{240} (%.240min)	15	6556 ± 1178	10	10085 ± 1433	3529 (-181 – 7238)	0.060
Total intestinal calorie delivery AUC						
Total intestinal calorie delivery AUC_{15} (kcal.15min)	15	360 ± 62	10	168 ± 76	-191 (-395 – 13)	0.064
Total intestinal calorie delivery AUC_{120} (kcal.120min)	15	13038 ± 1119	10	9763 ± 1346	-3275 (-6666 – 116)	0.057
Total intestinal calorie delivery AUC_{180} (kcal.180min)	15	23612 ± 1739	10	18428 ± 2107	-5184 (-10527 – 160)	0.056
Total intestinal calorie delivery AUC_{240} (kcal.240min)	15	34888 ± 2356	10	27830 ± 2866	-7057 (-14476 – 361)	0.060
Total intestinal calorie delivery per minute						
Intestinal calorie delivery per minute AUC_{15} (kcal/min.15min)	15	24.0 ± 4.1	10	11.2 ± 5.1	-12.8 (-26.3 – 0.8)	0.064
Intestinal calorie delivery per minute AUC_{120} (kcal/min.120min)	15	234.6 ± 24.2	10	161.5 ± 29.3	-73.1 (-157.3 – 11.2)	0.078
Intestinal calorie delivery per minute AUC_{240}	15	359.9 ± 29.8	10	264.4 ± 36.2	-95.5 (-192.3 – 1.3)	0.053

(kcal/min.240min)						
3-OMG						
3-OMG peak (mmol/L)	14	0.460 ± 0.040	14	0.426 ± 0.040	-0.034 (-0.106 – 0.038)	0.321
3-OMG AUC_{60} (mmol/L.60min)	13	14.4 ± 1.7	13	12.8 ± 1.6	-1.6 (-6.3 – 3.1)	0.471
3-OMG AUC_{120} (mmol/L.120min)	14	38.5 ± 4.0	14	35.7 ± 4.0	-2.8 (-11.6 – 6.1)	0.508
3-OMG AUC_{240} (mmol/L.240min)	14	81.6 ± 7.6	14	76.3 ± 7.6	-5.4 (-20.1 – 9.3)	0.437
Blood glucose						
Blood glucose baseline (mmol/L)	17	7.1 ± 0.4	16	6.7 ± 0.5	-0.4 (-1.6 – 0.7)	0.435
Blood glucose peak (mmol/L)[a]	17	10.1 ± 0.3	16	9.7 ± 0.3	-0.4 (-1.3 – 0.5)	0.364
Blood glucose AUC_{60} (mmol/L)[a,b]	17	8.7 ± 0.2	16	8.4 ± 0.3	-0.3 (-1.1 – 0.4)	0.347
Blood glucose AUC_{120} (mmol/L)[a,b]	15	8.7 ± 0.3	16	8.5 ± 0.3	-0.2 (-0.9 – 0.6)	0.661
Blood glucose AUC_{240} (mmol/L)[a,b]	15	7.8 ± 0.2	15	8.0 ± 0.2	0.2 (-0.6 – 0.9)	0.662

3-OMG: 3-O-Methyl-D-gluco-pyranose, AUC: Area under the curve, CI: Confidence interval, SEM: Standard error of the mean

[a] *Adjusted for baseline blood glucose*

[b] *Scaled for study duration*

Figure legends:

Figure 1: CONSORT diagram for patient enrolment

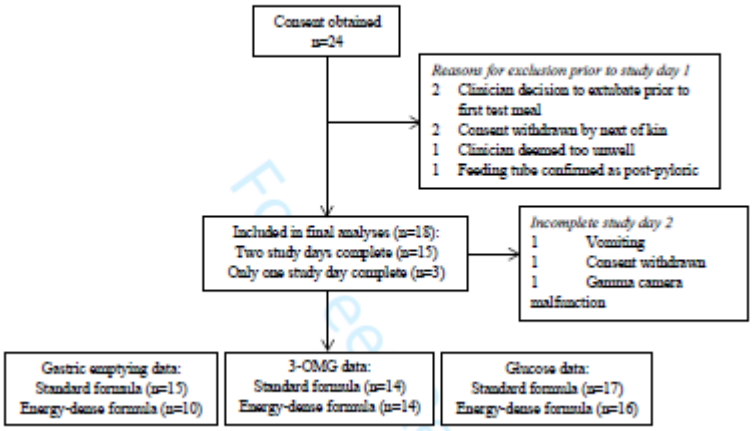


Figure 2: Gastric retention.

Gastric retention (%) of test meal measured with scintigraphy in patients receiving standard formula (filled circles) (n=15) and energy-dense formula (open circles) (n=10). Gastric retention (%) at 120 mins: 17.0 ± 5.9 vs 32.5 ± 7.1 %; mean difference 12.7 (90% CI 0.8 – 30.1); p=0.085. Data are presented as mean ± standard error.

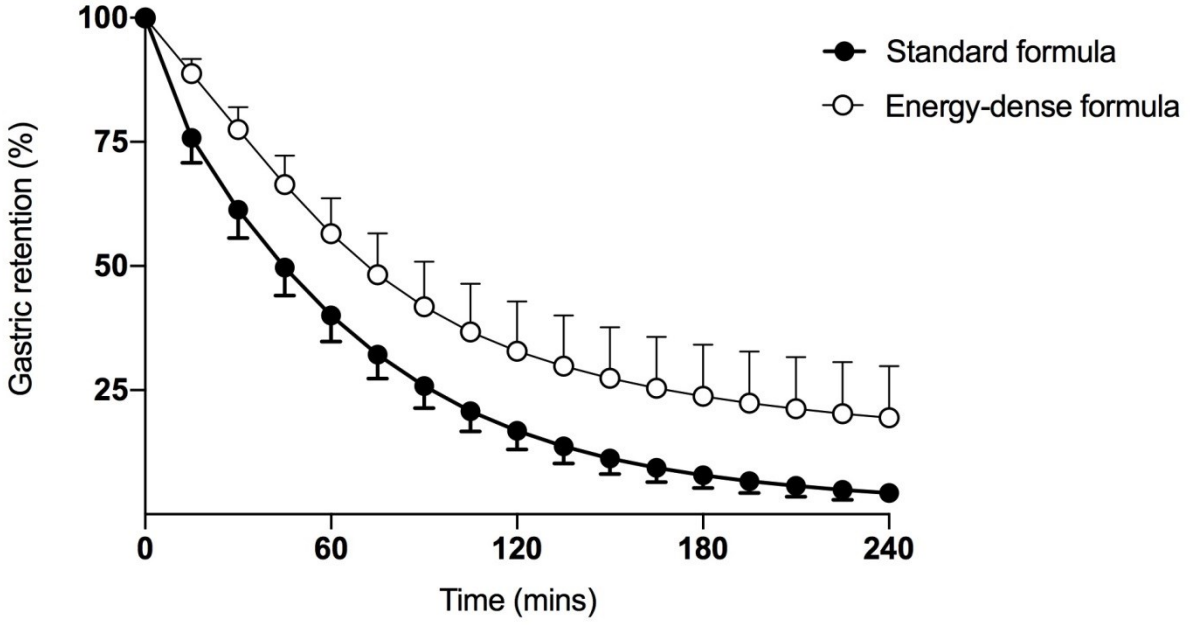
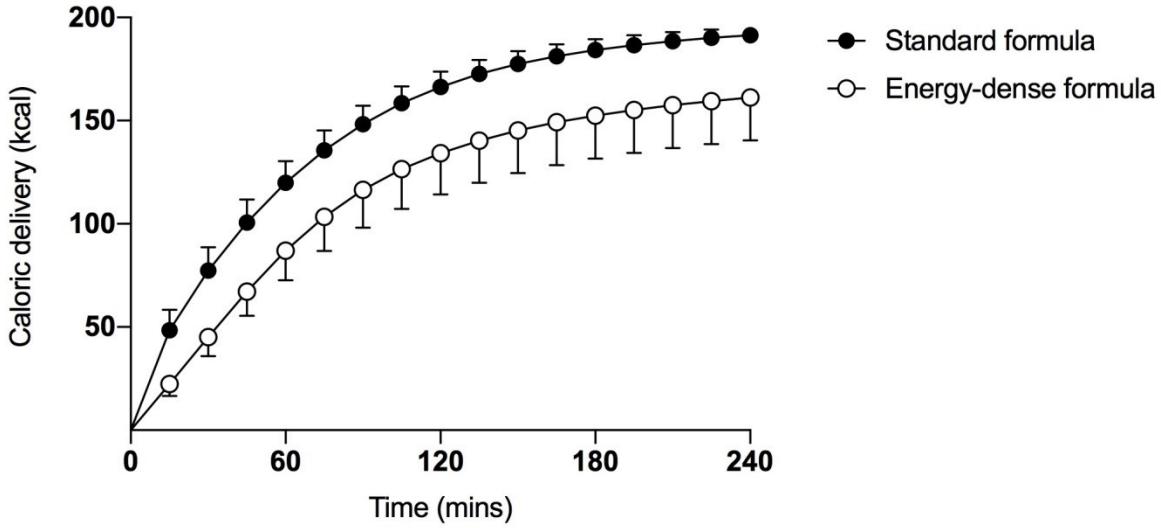


Figure 3a: Total intestinal calorie delivery (kcal).

Rate of total intestinal calorie delivery was similar in patients receiving standard formula (filled circles) (n=15) and energy-dense formula (open circles) (n=10). Calorie delivery area under the curve from baseline to 120 min: 13038 ± 1119 vs 9763 ± 1346 kcal.120min; difference -3275 (95% CI -6666 – 116) kcal.120min; p=0.057. Data are presented as mean ± standard error.



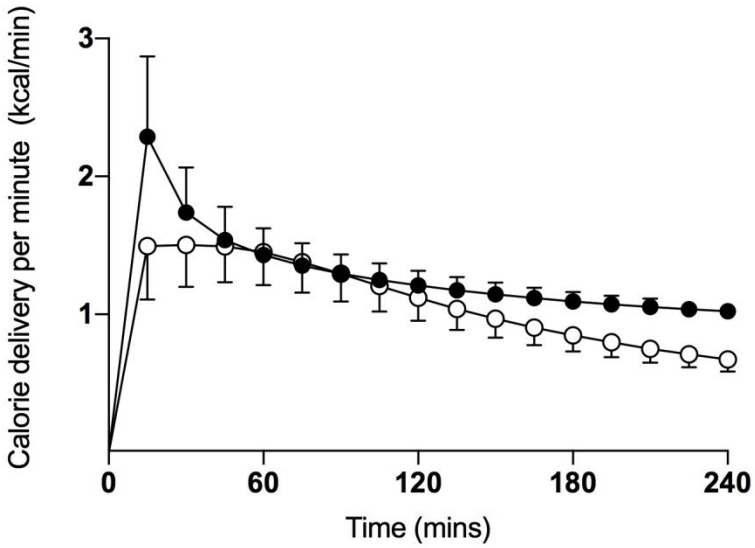


Figure 3b: Intestinal calorie delivery per minute (kcal/min).

The rate of intestinal calorie delivery per unit time was similar in patients receiving standard formula (filled circles) (n=15) and energy-dense formula (open circles) (n=10). Calorie delivery per minute area under the curve from baseline to 120 min: 235 ± 24 vs 162 ± 29 kcal/min.120min; difference -73 (95% CI -157 – 11) kcal/min.120min; p=0.078. Data are presented as mean ± standard error.

Figure 4: 3-OMG concentration.

Peak 3-OMG concentrations and 3-OMG area under the concentration curve at 60, 120 and 240 mins were similar in patients receiving standard formula (filled circles) (n=15) and energy-dense formula (open circles) (n=10) (all p>0.3). Data are presented as mean ± standard error of the mean.

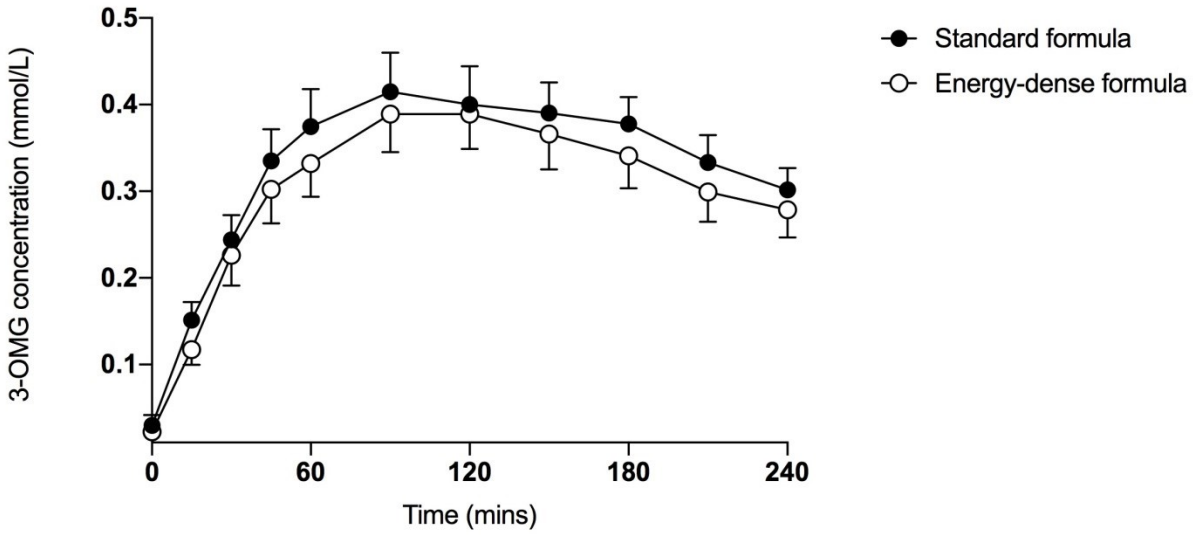
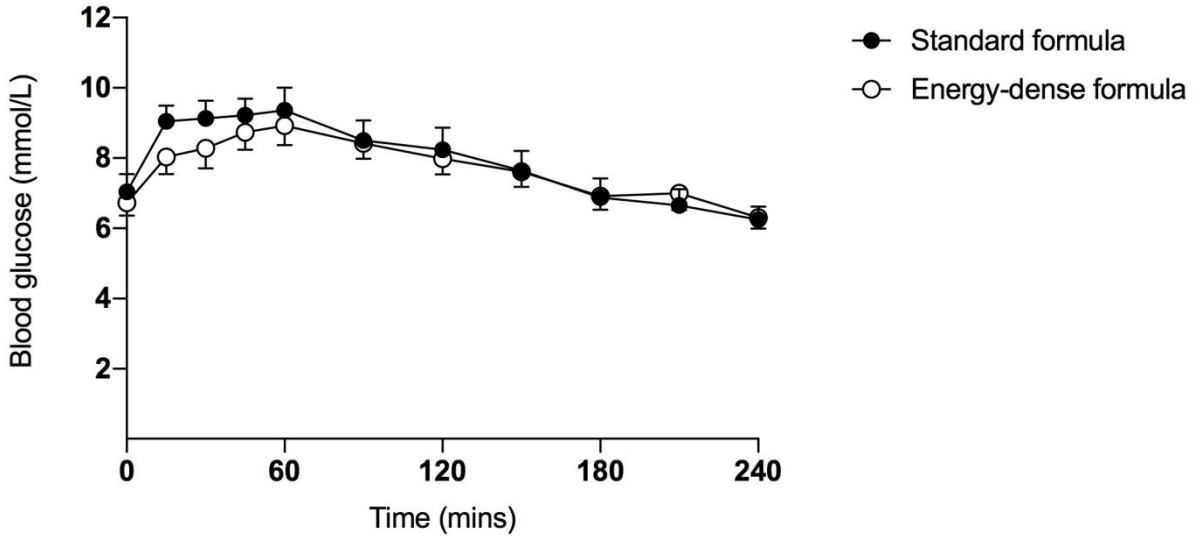


Figure 5: Blood glucose concentrations.

There were no differences in baseline, peak or AUC_{120} blood glucose between the standard and energy-dense formula (all p>0.3).



Supplementary Materials