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Original article

The effect of a low carbohydrate formula on glycaemia in critically ill enterally-fed adult patients with hyperglycaemia: A blinded randomised feasibility trial

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SUMMARY

Background: Enteral nutrition is a source of carbohydrate that may exacerbate hyperglycaemia. Its treatment, insulin, potentially exacerbates glycaemic variability.
Methods: This was a prospective, parallel group, blinded, randomised feasibility trial. Patients were eligible if 18 years or over when admitted to the intensive care unit and receiving enteral nutrition (EN) exclusively with two consecutive blood glucose > 10 mmol/L. A standardized glucose management protocol determined administration of insulin. Key outcome measures were insulin administered and glycaemic variability (coefficient of variation) over the first 48 h.
Results: 41 patients were randomized to either standard EN (14.1 g/100 mL carbohydrate; n = 20) or intervention EN (7.4 g/100 mL carbohydrate; n = 21). Overall 59% were male, mean (±SD) age of 62.3 years ± 10.4, APACHE II score of 16.5 ± 7.8 and a median (IQR) Body Mass Index 29.0 kg/m^2 (25.2–35.5). Most patients (73%) were mechanically ventilated. Approximately half (51%) were identified as having diabetes prior to ICU admission. Patients in the intervention arm received less insulin over the 48 h study period than those in the control group (mean insulin units over study period (95% CI) 45.0 (24.4–68.7) vs. 107 (56.1–157.9) units; p = 0.02) and had lower mean glycaemic variability (12.6 vs. 15.9%, p = 0.01). There was a small difference in the mean percentage of energy requirements met (intervention: 72.9 vs. control: 79.1%; p = 0.4) or protein delivered (78.2 vs. 85.4%; p = 0.3).
Conclusions: A low carbohydrate formula was associated with reduced insulin use and glycaemic variability in enterally-fed critically ill patients with hyperglycaemia. Further large trials are required to determine the impact of this formula on clinical outcomes.
Registered under Australian and New Zealand Clinical Trials Registry, ANZCTR number: 12614000166673.

1. Introduction

Nutritional therapy is a component of standard care for critically ill patients [1,2] and is most frequently delivered in the form of a liquid formula administered through a nasogastric or orogastric tube [3]. Commercially available formulae used within the acute

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setting are, in most instances, nutritionally complete and comprise key macro- and micronutrients with carbohydrate being one of its major constituents. Despite absorption of carbohydrate being impaired during critical illness when compared to health, the glycaemic response to enteral carbohydrate is greater and sustained for longer [4,5].

There is a high prevalence of acute hyperglycaemia in the critically ill, even in the absence of pre-existing diabetes [6,7]. The underlying mechanisms driving acute glucose intolerance are complex [5,8]. However, acute hyperglycaemia is strongly associated with increased mortality and morbidity in the critically ill [6,7,9]. Based on these associations, current clinical practice guidelines include recommendations that acute hyperglycaemia is treated with insulin [10]. However, exogenous insulin is associated with increased risk for hypoglycaemia and variability in blood glucose, which are also associated with adverse outcomes [11–13].

Exogenous carbohydrate provision is associated with increased insulin use [13]. In other settings a reduction in the carbohydrate content of nutritional formula has attenuated glycaemic excursions and requirement for exogenous insulin [14–16]. Accordingly, we hypothesised that provision of a low carbohydrate and low glycaemic index diabetes specific formula would reduce insulin requirements and glycaemic variability in critically ill patients when compared to patients receiving a standard formula over a 48 h period. A range of secondary scientific and feasibility outcomes of study processes were measured including overall blood glucose control, the adequacy of the inclusion and exclusion criteria, consent processes, recruitment rate and patient retention to 48 h. Exploratory tertiary outcomes included length of ICU and hospital stay and mortality.

2. Methods

2.1. Protocol

The study protocol was registered prior to study commencement (Australian and New Zealand Clinical Trials Registry, ANZCTR number: 12614000166673) and was published in full prior to completion of recruitment [17]. An abridged version is detailed below. This manuscript reports primary, secondary and key exploratory outcomes between control (Nutrison Protein Plus Multifibre®) and intervention (low carbohydrate formula Glucerna Select®) groups. Patients recruited to a third arm for the purpose of a biomarker sub-study which will be reported separately.

The protocol was developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT 2013) [18] and the Consolidated Standards for Reporting of Trials CONSORT Guidelines [19]. It complies with the Australian National Statement on Ethical Conduct in Human Research [20].

2.2. Study design

2.2.1. Study site

This was a single centre, prospective, parallel group, blinded and randomised feasibility trial carried out over a 3 year period. It was conducted at 2 Intensive Care Units (ICU) at a single hospital, Mater Health, Brisbane, Australia. The Mater ICUs are combined adult medical/surgical/maternity units comprising 26 beds in total with over 2000 admissions per year. The intensive care physicians work across both ICUs where all clinical care is governed by the same policies and procedures.

2.2.2. Patients

Patients requiring insulin to treat hyperglycaemia, defined as 2 consecutive blood glucose readings $\geq$10 mmol/L, while receiving enteral nutrition were deemed eligible for the study. This was regardless of pre-existing diabetes mellitus status. Exclusion was determined by the following: declined consent, patients under 18 years of age or deemed to be clinically inappropriate by the treating physician. Either the patient (if alert) or the legally authorised representative was approached for consent to enrol in the study. The protocol was approved by the Mater Human Research Ethics Committee and The University of Queensland Research Ethics Committee (Mater HREC Approval: HREC/14/MHS/55; UQ HREC: Approval 2014001353).

2.2.3. Randomisation

A computer-generated block randomisation sequence was developed and this allocation information placed in sequentially ordered opaque envelopes available to clinical staff after recruitment.

2.2.4. Insulin prescription

Clinical management of insulin requirements proceeded as usual regardless of study participation. Bedside nurses acted upon blood glucose concentrations that were measured using a blood gas analyser (ABL 800-FLEX-Radiometer) or point of care glucometer (Freestyle optimum Neo-H). For all participants the insulin protocol aimed to achieve target blood glucose concentrations of between 6 and 10 mmol/L. The protocol included 4 different sliding scales (1-lowest, 4-highest) used in a stepwise escalation dependent upon blood glucose readings (Supplemental appendix 1). Patients commenced on the first level if they had 2 consecutive readings of >10 mmol/L and were escalated to the next level each time they had 2 consecutive readings of >12 mmol/L. Each patient's insulin dose and frequency of measurements were dependent upon their level in the protocol. The higher the level, the greater the insulin dose and the more frequent the blood glucose checks.

2.2.5. Nutrition prescription

Target rates for each formula were calculated using weight based estimations − 25 kcal/kg body weight (BW) for energy and 1.2 g/kg BW for protein [1]. Adjusted ideal body weight (AIBW = ((Actual weight−weight at BMI 25 kg/m^2)*0.25) + weight at BMI 25 kg/m^2) was used for patients with a BMI>25 kg/m^2 [21,22]. Pre-calculated weight based target rates for each formula, denoted as either formula A, B or C to maintain blinding, were included in the allocation envelopes. Aside from the target rate, all other aspects of enteral nutrition delivery, including rate increases and gastric residual volumes monitoring and return, were managed as per the unit's standard feeding protocol (supplemental appendix 2).

2.2.6. Study procedure

Once patient consent was obtained and the randomisation arm assigned, patients received one of two formulae − 1)Control liquid nutrient, representative of a standard macronutrient enteral formula, (Nutrison Protein Plus Multifibre®, 1.25 kcal/mL, 6.3 g/100 mL protein, 14.1 g/100 mL carbohydrate, 4.9 g/100 mL fat, **CON**) or 2) Intervention liquid nutrient-a low carbohydrate formula, (Glucerna Select®, 1 kcal/mL, 5 g/100 mL protein, 7.4 g/100 mL carbohydrate, 5.4 g/100 mL fat, **INT**). All patients remained on the allocated formula until tube feeds were no longer required or if there was a change in their clinical condition which required an alternate non study formula. Blinding of the formula, as outlined in more detail within the published protocol [17], was carried out by the ICU pharmacist. All formulae were concealed by means of a labelled opaque bag.

2.3. Data collection

2.3.1. Primary outcome

The trial primary outcome was the average hourly insulin dose while receiving enteral nutrition up to a maximum period of 48 h post randomisation. Where the time on nutrition formula was shorter than 48 h, only the insulin rates while on nutrition were included.

2.3.2. Secondary clinical outcomes

Glycaemic variability was summarized as the blood glucose coefficient of variation [13,23]. Other measures of glucose control included mean blood glucose levels and percentage of readings within target blood glucose range. Tolerance of enteral nutrition was assessed due to the differing fat content and osmolality of formulae (Fat: CON -34% vs. INT – 48% of caloric composition; Osmolality 360 vs. 450mOsmol/kg H_2O) using the following surrogate markers: 1) a gastric residual volume threshold of $\geq$300 mL, 2) prokinetic administration or 3) presence of diarrhoea, defined as 3 or more loose or liquid stools per day [24,25]. Ability to meet nutritional requirements was also assessed in the time intervals where feeding was administered, calculated as nutrition received relative to estimated nutrition requirements (Energy requirement: 25 kcal/kg BW or AIBW/day and Protein requirement: 1.2 g/kg BW or AIBW/day).

2.3.3. Secondary feasibility outcomes

The adequacy of inclusion and exclusion criteria in determining patient eligibility was assessed using the number of patients deemed clinically inappropriate for inclusion by clinicians as a surrogate marker. The number of patients reaching 48 h on formula post randomisation was used to determine if the inclusion criteria should detail expected duration of artificial nutrition support. Recruitment rates were assessed based on number of patients screened who then consented and were enrolled into the study.

2.3.4. Exploratory measures

Clinical outcome data such as duration of ventilation (hours between intubation and extubation or alternatively spontaneous breathing with tracheostomy in situ), ICU length of stay (LOS) and hospital LOS were determined using hospital records. A 28 day mortality check by phone call or hospital record was undertaken. Mortality data was censored for those patients who could not be contacted by phone at 28 days but were discharged alive from hospital.

2.4. Statistical analyses

There was a minimum target recruitment of 19 patients per arm to detect with 80% power at alpha 0.05 a mean difference of 21.5 units of insulin per day assuming a common standard deviation of 22.5 units (modelled off a study by Mesejo et al. [26]). All analyses were conducted using R: A Language and Environment for Statistical computing and Stata Statistical Software [27,28]. Patient characteristics are summarised using frequencies and percentages for categorical variables and mean (±SD) or median (IQR) for continuous variables. Units of insulin administered at each point of measurement were examined as repeated measures using a linear mixed model with a random intercept at the level of each patient and a restricted maximum likelihood approach. Mean blood glucose and probability of blood glucose outside of target range were analysed using linear and binary logistic mixed models respectively adjusted for time. Student's t-test was used to assess differences between groups for glycaemic variability summarized as the coefficient of variation, total carbohydrate from feed and patients' ability to meet protein and energy requirements. Duration of ventilation, ICU length of stay and hospital length of stay were analysed using a Mann–Whitney U test. Fisher's exact test was used to compare the proportions of tolerance of nutrition and mortality between groups. The level of statistical significance was set at 0.05.

3. Results

3.1. Patient characteristics

Patients were screened and recruited between February 2015 and March 2018. Forty-one patients were included in the final analyses (Fig. 1). Patients were similar between groups for age, body mass index, sex, pre-admission diabetes status, steroid prescription and duration of time that they received nutrition formula (Table 1).

3.2. Primary outcome: insulin use

The low carbohydrate formula with a lower mean insulin administration rate per hour (**INT:** 1.01 (95% CI: 0.27–1.75) vs. **CON:** 2.31 (95% CI: 1.55–3.07) units/hour, Δ 1.30 units/hour (95% CI: 0.24–2.36), p = 0.017); and lower total units over 48 h (**INT:** 45.0 (95% CI: 21.4–68.7) vs. **CON:** 107.0 (95% CI: 56.1–157.9) units/48h, Δ 61.9 units/48h (95% CI 8.5–115.3); p = 0.02). This was visualized for the entirety of the study period (Fig. 2).

3.3. Secondary clinical outcomes

3.3.1. Glycaemic variability and glycaemic control

Patients allocated to receive the low carbohydrate formula had less glycaemic variability than patients receiving standard macronutrient formula as shown in Fig. 3 (**INT**: 12.6% (95% CI: 12.2–14.1) vs. **CON:** 15.9% (95% CI: 12.7–18.1%), Δ 3.3 (95% CI: 0.6–5.6); p = 0.01). The INT group had a lower mean blood glucose level and a lower probability of blood glucose levels outside the target range (6–10 mmol/L) when compared to the CON group (Table 2). There were no reported episodes of hypoglycaemia (<4.5 mmol/L) in either group.

3.3.2. Tolerance and ability to meet nutritional requirements

There was no evidence of differences between groups for tolerance of liquid nutrient formula and a relatively small difference in the percentage of estimated requirements met (Table 2). Three patients in the INT arm were prescribed and hence received one third of their estimated requirements for clinical reasons unrelated to tolerance. Excluding these patients resulted in patients receiving similar amounts of their protein and energy requirements between groups. The difference between groups for both insulin use and glycaemic variability remained statistically significant (Supplemental Appendix 3).

3.4. Secondary feasibility outcomes

3.4.1. Eligibility criteria

Thirty -two out of the 107 (30%) patients that met all inclusion criteria were excluded based on the clinical opinion of the treating team. Reasons for exclusion were organ failures requiring disease specific feeds or renal replacement therapy, potential imminent mortality and likely extubation within 24 h.

3.4.2. Consent process and recruitment rate

Twenty-one (20%) patients or their legally authorised representatives declined consent.

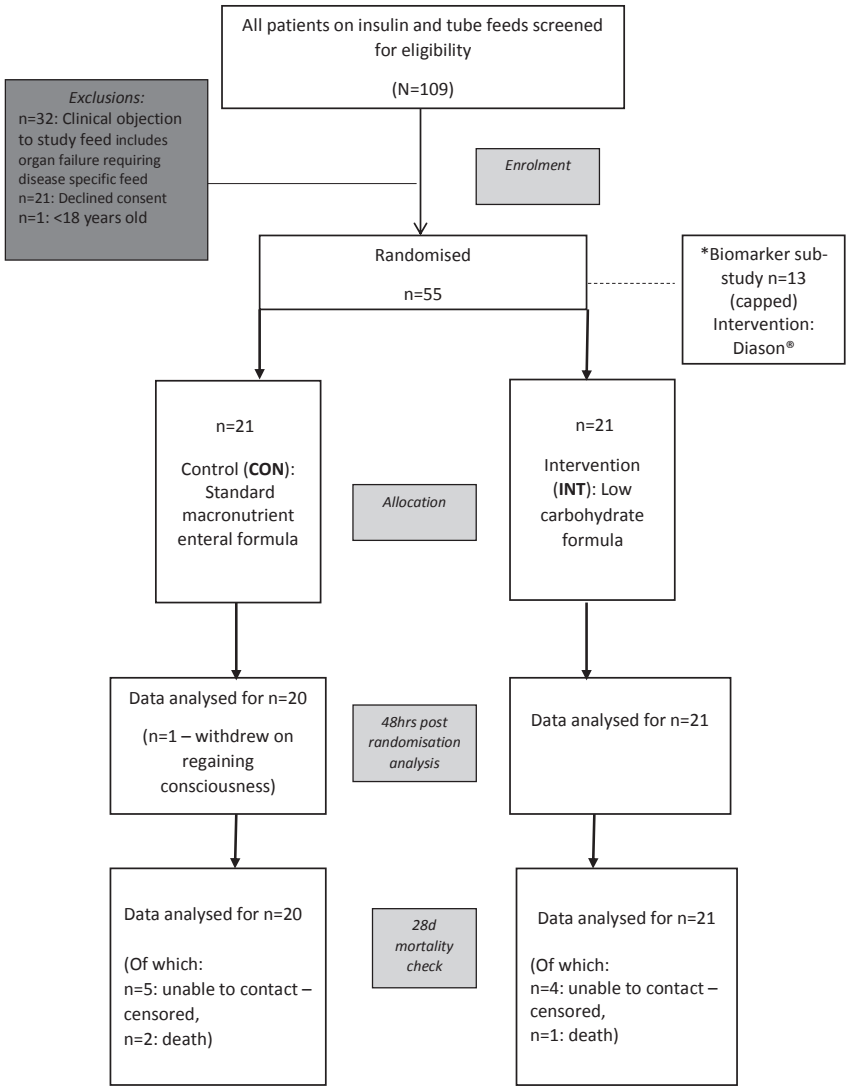

Fig. 1. Patient Flow Diagram. *Patients randomised to the intervention group receiving Diason® formed part of a sub-study which has not been described in this study.

3.4.3. Retention

Eleven out of 41 (27%) patients enrolled in the study did not continue to receive study feed for the entire 48 h period. Reasons for cessation of formula before 48 h included preparation for extubation, extubation and removal of feeding tube as well as discharge from ICU.

3.5. Exploratory outcomes

3.5.1. Morbidity and mortality

There were no obvious differences for clinical outcomes (Table 2).

4. Discussion

The major finding of this study is that in enterally-fed critically ill patients a low carbohydrate formula when compared to a standard macronutrient formulae was associated with noticeably reduced insulin administration and attenuated glycaemic variability. Furthermore, patients within the INT arm had a lower mean blood glucose level and percentage of blood glucose readings outside the target range (6–10 mmol/L) as compared to patients in the CON group. There was a small difference in caloric and protein administration explained by clinical necessity for 3 patients to receive reduced nutrition and no evidence of different feed-tolerance with the low carbohydrate formula.

The optimal amount of energy and protein that should be administered in the acute phase of critical illness remains contentious [29,30]. While the macronutrient content of liquid nutrient has received little attention, the proportion of carbohydrate delivery may be important. Hyperglycaemia, as a result of excess energy delivery, is strongly associated with increased duration of ventilation [31,32] and mortality [6]. It is plausible that excess carbohydrate and hyperglycaemia are confounders, masking potential benefits of increased energy and protein delivery. Energy and protein targets could be met with low carbohydrate formulae but the efficacy of these formulae in improving overall glycaemic control requires further investigation [1,33].

4.1. Comparison to previous studies

Previous trials have evaluated the use of low carbohydrate formulae. Mesejo and colleagues carried out a prospective, multicentre trial of 157 medical-surgical patients who were randomised to receive one of three feeds - two varying low carbohydrate formulae and a standard high protein formula [34]. The primary endpoint was

Table 1
Patient characteristics at randomisation.

	CON (N = 20)	INT (N = 21)
Age (years), mean (SD)	62.2 (11.3)	62.4 (9.9)
BMI (kg/m^2), median (IQR)	27.3 (25.3–36.0)	29.4 (25.1–31.5)
Gender		
Male, n (%)	11 (55)	13 (62)
Female, n (%)	9 (45)	8 (38)
APACHE II score, mean (SD)	15 (7.7)	17 (7.9)
Admission diagnosis		
Surgical, n (%)	11 (55)	9 (43)
Respiratory, n (%)	6 (30)	7 (33)
Haematology, n (%)	1 (5)	1 (5)
Neurology, n (%)	2 (10)	4 (19)
Mechanical Ventilation, n (%)	13 (65)	17 (81)
Duration of mechanical ventilation (hours), median (IQR)	160 (106–219)	141 (93–225)
[a]Presence of sepsis during study period, n (%)	7 (35)	4 (19)
Steroid use, n (%)	10 (50)	11 (52)
[b]High dose, n (%)	8 (80)	10 (91)
Not high dose, n (%)	2 (20)	1 (9)
[c]Pre-admission diabetes, n (%)	11 (55)	10 (48)
Duration of feeding time (hours), mean (SD)	44.1 (9.5)	43.4 (9.3)
Estimated energy requirements (kilojoules), median (IQR)	8190 (7455–9008)	8085 (7665–9135)
Estimated protein requirements (grams), median (IQR)	86 (84–97)	92 (87–103)
Additional intravenous glucose over study period (g, SD)	16.5 (54.7)	17.5 (57.2)

APACHE, Acute Physiologic Assessment and Chronic Health Evaluation; BMI, body mass index; IQR, interquartile range; kg/m^2, kilograms per meter squared; SD, standard deviation.
[a] Includes both sepsis on admission and sepsis at time of randomisation.
[b] Dose categorized as per PG-SGA assessment tool as described in published protocol.
[c] Determined based on a documented diagnosis on ICU admission.

insulin administered to maintain capillary blood glucose levels between 6.1 and 8.3 mmol/L. Patients on the low carbohydrate formulae required less insulin than the high protein feed.

More recently van Steen and colleagues published their study of 107 patients randomised to either a standard energy dense feed (15% protein, 48% carbohydrate) or a low carbohydrate, energy dense feed (22% protein, 33% carbohydrate) [35]. Blood glucose levels were monitored using subcutaneous continuous glucose monitoring and maintained between 6 and 9 mmol/L using a sliding scale algorithm. Investigators did not find any difference between groups for glycaemic variability or overall units of insulin except on day 2 of treatment where less units of insulin were administered in the low carbohydrate formula group. This difference in findings could be related to differences in nutrition provision and glucose monitoring and control. Patients received 35–55% less calories on average when compared to our patient cohort. Increased caloric delivery is associated with increased insulin doses [13]; therefore it is reasonable to postulate that if patients were matched for caloric delivery, their insulin requirements would increase subsequently having a flow on effect on exogenous insulin administration and glycaemic variability [36]. Additionally, van Steen and colleagues utilised a subcutaneous continuous glucose monitoring device measuring interstitial glucose. Accuracy using this method is reliant on adequate perfusion which is influenced by hydration, blood flow and metabolic rate [37,38], all of which are affected in critically ill patients.

Rice et al. (2018) conducted a multicentre trial in overweight and obese, mechanically ventilated patients in which patients were

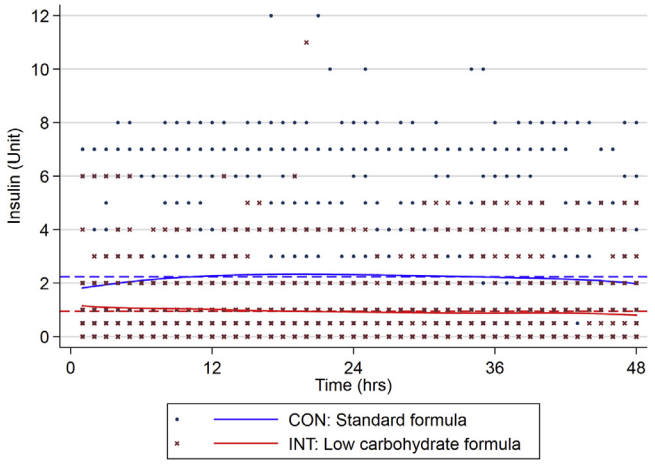

Fig. 2. Scatter plot of units of insulin per hour over time by group and Locally Weighted Scatterplot Smoothing provides a visual depiction of the difference in units of insulin per hour.

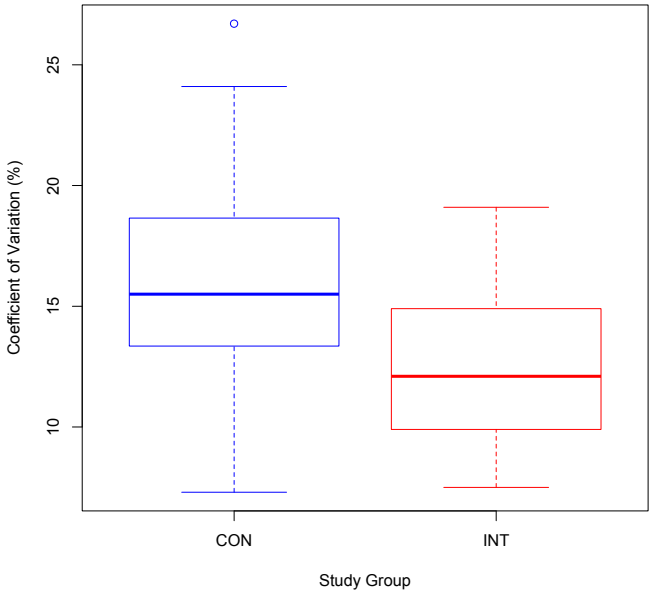

Fig. 3. Box plot of glycaemic variability defined as coefficient of variation (%) of blood glucose by group.

Table 2
Outcome data comparison between groups.

	CON (n = 20)	INT (n = 21)	p value
Glycaemic control			
Mean blood glucose (mmol/L, 95% CI)	10.1 (9.4–10.7)	8.7 (8.0–9.3)	0.002
Probability of blood glucose outside of range (6–10 mmol/L), % (95% CI)	48 (35–61)	25 (15–35)	0.005
Average number of blood glucose readings per patient (SD)	20.6 (5.7)	18.7 (5.0)	0.3
Tolerance of EN			
Incidence of Gastric Residual Volumes > 300 mL, n (%)	3 (15)	2 (9.5)	0.7
Prokinetic use, n (%)	3 (15)	5 (23.8)	0.7
Diarrhoea, n (%)	3 (15)	2 (9.5)	0.7
Nutrition received (over 48 h)			
Average energy received (kilojoules, SD)	11528 (3281)	10901 (4000)	0.6
Average protein received (g, SD)	135.8 (38.6)	130.7 (47.9)	0.7
Average carbohydrate received (g, SD)	294.9 (85.5)	191.1 (70.7)	<0.001
Average percentage of energy requirements received (%, SD) [a]over feed time	79.1 (21.5)	72.9 (23.7)[b]	0.4
Average percentage of protein requirements received (%, SD) [a]over feed time	85.2 (22.3)	78.2 (22.9)[b]	0.3
Clinical outcomes			
Duration of ventilation (hours, median (IQR))	160 (106–219)	141 (94–184)	0.7
ICU length of stay (days, median (IQR))	8 (6–11)	7 (4–11)	0.8
Hospital length of stay (days, median (IQR))	15 (11–20)	18 (14–30)	0.1
28 day mortality (n, %)	2 (10)	1 (5)	0.6

BW, body weight; ICU, intensive care unit; IQR, interquartile range; Kcal, kilocalories; kg, kilograms; SD, standard deviation.
[a] Over feed time: Percentage of requirements met based on duration patient on formula rather than full 48 h timeframe.
[b] Three patients intentionally received a third of their target nutrition as per treating teams.

randomised to either a low carbohydrate, very high protein feed or a standard high protein feed with nutrition prescription based on achieving a target for protein of 1.5 g/kg of body weight [39]. The primary endpoint for this study was the difference in mean rate of blood glucose levels outside of the range of 6.1–8.3 mmol/L. A planned interim analysis showed no difference between groups for primary outcome when recruitment had reached 50% of target and the trial had to be ceased for futility. Further analyses did find a reduction in number of times insulin was administered but not of total units overall. There are two key differences with regards to study design when compared to the current study. The inclusion criteria for the study by Rice et al. meant that BMI was greater (Rice et al., mean (SD): Control = 33 (5.8) and Experimental = 33.4 kg/m^2 (4.6) vs. Current study, median (IQR): CON = 27.3 (25.3–36.0) and INT = 29.4 kg/m^2 (25.1–31.5)). In addition patients deliberately received less than estimated resting energy equation (16 kcal/kg ideal body weight vs. 25 kcal/kg adjusted ideal body weight.

There is ongoing pursuit of research to define optimal glucose levels and methods that are best to achieve this in critically ill patients with hyperglycaemia. Intravascular continuous glucose monitoring devices in conjunction with computer generated insulin sliding scales hold merit in achieving this [40]; however, these are costly resources that are not easily accessible for the majority of ICUs. Instead, our study findings as well others suggest that the use of LCF, when aiming for target nutrition rate, may be an effective strategy to reduce exogenous insulin administration [34,41] and glycaemic variability [34]. The implications of this reduction in both insulin and glycaemic variability needs to be determined in a larger trial adequately powered for clinical end-points.

The macronutrient composition of delivered nutrition formula should be considered as an entirety. Low carbohydrate formulae tend to have a greater fat content than standard formula. We did not find any evidence of differing tolerance despite the possibility that increased fat content of formula delays gastric emptying [42] and leads to greater intolerance. This warrants further exploration in a larger study as the recently reported TARGET trial showed that patients receiving an energy-dense formula had greater gastrointestinal intolerance than those on a standard macronutrient formula. With over 4,000 patients included in TARGET, the trial would have adequate power to identify secondary effects that are not apparent within a smaller feasibility study [29].

4.2. Feasibility and design

Recruitment was slower than anticipated. Reasons included patients excluded based on clinician judgment and a 20% declined consent rate. Missing data was also an issue with not all participants receiving EN for the entire 48 h time period.

The approach to blinding was a pragmatic one for the purpose of this initial feasibility study as outlined in the protocol [17]. A larger and more substantially funded study would ideally apply robust procedures whereby manufacturers provide formulae that are well matched for energy density and presentation.

4.3. Limitations

The intensive care insulin protocol allows the use of either arterial blood used in glucometer, arterial blood gas result or capillary measures of glucose. We did not interfere with the usual glucose/insulin protocol. There is a tendency for slight variation in blood glucose measurements between techniques [43]. This study's methodology incorporated randomization and allocation concealment which should mitigate this potential confounder.

Investigators acknowledge that glycaemic variability can be influenced by the insulin protocol itself. While that is a consideration for interventions designed to optimise glucose control, it fell outside the scope of this particular study. The aim of this trial was to investigate whether or not a change in nutrition formula had an impact on glycaemic variability in the context of current clinical practices.

The main limitation of this study, inherent to feasibility trials, is the small cohort studied. In such a small sample it is unlikely that any intervention will be associated with patient centred outcomes (duration of ventilation, length of stay or mortality).

4.4. Clinical significance

Administration of a low carbohydrate formula to enterally-fed critically ill patients was associated with reduced insulin administration. Exogenous insulin is a potent suppressant of autophagy [44,45] and can alter inflammatory processes [46]. It was also associated with a reduction in glycaemic variability. Strong relationships between greater glycaemic variability and mortality

have been reported [11,47,48]. This feasibility study had low power to detect any effect on patient centred outcomes such as duration of ventilation, length of stay (ICU and Hospital) or mortality.

Our findings provide clinicians with a simple and effective strategy to manage challenging blood glucose control in critically ill patients. This strategy, using a low carbohydrate formula in patients with hyperglycaemia, would be worth evaluating in further trials to determine any potential impact on outlined patient centred outcomes.

5. Conclusions

In critically ill patients with hyperglycaemia a low carbohydrate formula when compared to a standard polymeric formula was associated with reduced insulin administration and attenuated glycaemic variability. Further studies are warranted to investigate the implications of this reduction on clinical endpoints such as mechanical ventilation, length of stay and mortality.

Financial disclosures

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Conflict of interest

The authors have no conflict of interests to declare.

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RD, AT, JF and DS contributed to the conception and design of the research; AD, DT, JP and SO contributed to the design of the research; RD and DT contributed to the acquisition of data; RD, SO and JP contributed to the analysis of the data; RD, AD, JP, HB, SO and DS contributed to the interpretation of the data; and RD drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2019.02.013.

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