Comparison of sequential feeding and continuous feeding on the blood glucose of critically ill patients: a non-inferiority randomized controlled trial

Chang-Jie Ren[1], Bo Yao[2], Miao Tuo[1], Hui Lin[2], Xiang-Yu Wan[2], Xu-Feng Pang[2]

[1]The Department of Neurology in the Affiliated Hospital of Qingdao University, Qingdao, Shandong 266000, China;
[2]The Department of Critical Care Medicine in the Affiliated Hospital of Qingdao University, Qingdao, Shandong 266000, China.

Abstract

Background: Glucose control is an important aspect in managing critically ill patients. The goal of this study was to compare the effects of sequential feeding (SF) and continuous feeding (CF) on the blood glucose of critically ill patients.

Methods: A non-inferiority randomized controlled trial was adopted in this study. A total of 62 patients who were fed enteral nutritional suspension through gastric tubes were enrolled. After achieving 80% of the nutrition target calories (25 kcal·kg^{-1}·day^{-1}) through CF, the patients were then randomly assigned into SF and CF groups. In the SF group, the feeding/fasting time was reasonably determined according to the circadian rhythm of the human body as laid out in traditional Chinese medicine theory. The total daily dosage of the enteral nutritional suspension was equally distributed among three time periods of 7 to 9 o'clock, 11 to 13 o'clock, and 17 to 19 o'clock. The enteral nutritional suspension in each time period was pumped at a uniform rate within 2 h by an enteral feeding pump. In the CF group, patients received CF at a constant velocity by an enteral feeding pump throughout the study. Blood glucose values at five points (6:00/11:00/15:00/21:00/1:00) were monitored and recorded for seven consecutive days after randomization. Enteral feeding intolerance was also recorded. Non-inferiority testing was adopted in this study, the chi-square test or Fisher test was used for qualitative data, and the Mann-Whitney *U* test was used for quantitative data to determine differences between groups. In particular, a repeated measure one-way analysis of variance was used to identify whether changes in glucose value variables across the time points were different between the two groups.

Results: There were no significant demographic or physiological differences between the SF and CF groups ($P > 0.050$). The average glucose level in SF was not higher than that in CF (8.8 [7.3–10.3] *vs.* 10.7 [9.1–12.1] mmol/L, $Z = -2.079$, P for non-inferiority = 0.019). Hyperglycemia incidence of each patient was more common in the CF group than that in the SF group (38.4 [19.1–63.7]% *vs.* 11.8 [3.0–36.7]%, $Z = -2.213$, $P = 0.027$). Hypoglycemia was not found in either group. Moreover, there was no significant difference during the 7 days in the incidence of feeding intolerance ($P > 0.050$).

Conclusions: In this non-inferiority study, the average blood glucose in SF was not inferior to that in CF. The feeding intolerance in SF was similar to that in CF. SF may be as safe as CF for critically ill patients.

Trial Registration ClinicalTrials.gov, NCT03439618; https://clinicaltrials.gov/ct2/show/record/NCT03439618

Keywords: Intensive care unit; Enteral feeding; Blood glucose; Feeding intolerance

Introduction

It is recommended that intensive care unit (ICU) patients start enteral feeding as long as gastrointestinal function allows. However, most critically ill patients have physiological dysfunctions and poor intestinal tolerance and are prone to feeding complications. Continuous feeding (CF), due to the long duration of infusion, may have benefits in reducing enteral feeding complications. Compared with intermittent feeding, CF is thought to be better tolerated by critically ill patients, providing better control of blood glucose and a lower incidence of feeding complications such as diarrhea, vomiting, and aspiration.[1] However, in recent years, according to relevant literature reports, continuous enteral nutrition feeding methods have been found to have problems, such as disturbing biological, protein synthesis, gastric volume, and physiological functions, since CF does not conform to the physiological state of the human body and violates the natural biological rhythms.[1,2] Moreover, with the deepening of research

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Chang-Jie Ren and Bo Yao contributed equally to this work.

Correspondence to: Dr. Xu-Feng Pang, The Department of Critical Care Medicine in the Affiliated Hospital of Qingdao University, Jiangsu Road 16, Qingdao, Shandong 266000, China.
E-Mail: qdfyicuhl@163.com

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and an increase in the number of included cases, an increasing number of studies have shown that the benefits of enteral feeding and the complications of CF are the same as those of intermittent feeding.[3-5] A randomized three-way crossover pilot study of healthy volunteers showed no difference in gastric reflux between intermittent and CF.[3] For critically ill patients, CF and intermittent feeding have no differences in enteral feeding complications such as diarrhea, bloating, and vomiting.[4] No clinically relevant differences in glycemic variability (GV) or insulin use were found between bolus tube feeding and continuous tube feeding.[5]

Under normal physiological conditions, the circadian system readies the body for daytime feeding. The rate of gastric emptying and gastrointestinal motility is faster in the daytime than at night, with rates peaking in the morning, and gastric acid secretion also has an internal circadian rhythm.[6-8] Aligning feeding/fasting cycles with clock-regulated metabolic changes optimizes the metabolism, and animal studies have suggested that feeding at inappropriate times disrupts the circadian system organization and thereby contributes to adverse metabolic consequences and chronic disease development.[9] Here, we propose a new feeding method called sequential feeding (SF). In this SF, after the patients achieved 80% of the nutrition target calories (25 $kcal \cdot kg^{-1} \cdot day^{-1}$) through CF, then the feeding/fasting time is reasonably determined according to the circadian rhythm of the human body and the physiological movement of the digestive organs as laid out in traditional Chinese medicine theory. In traditional Chinese medicine theory, each human organ works regularly at different times throughout the day, and the best feeding times are 7 to 9 o'clock, 11 to 13 o'clock, and 17 to 19 o'clock. Therefore, this SF consists of an initial CF and subsequent intermittent feeding. We think this feeding method is more consistent with human physiological activities and is more suitable for critically ill patients.

Glucose is recognized as a proinflammatory mediator and can generate reactive oxygen species.[10] It can impair the immune system and increase the risk of infection.[11] High glucose levels and high GV, as well as hypoglycemia,[12] are also independent conditions associated with an increased risk of mortality in critical illness.[13,14] Therefore, glucose control is an important aspect in managing critically ill patients. As a physiological feeding mode, we hypothesized that SF will not increase the difficulty of glucose control. Therefore, the primary objective of this study was to determine if the average glucose in SF would not be higher than that in CF among critically ill patients.

Methods

Ethical approval

We performed a prospective, single-blinded, and non-inferiority randomized controlled trial in ICU at the Affiliated Hospital of Qingdao University. The trial was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University (No. QYFYKYLL 2018-16). This study is a part of a randomized controlled trial. All of the patients or their legally authorized representatives provided written informed consent.

Patients

This study was conducted on patients who were admitted to the ICU from May to December 2018. Patients newly admitted to the ICU and fed through gastric tubes were enrolled. Moreover, these patients needed to be able to tolerate ≥80% of the nutrition target calories (25–30 $kcal \cdot kg^{-1} \cdot day^{-1}$) with enteral feeding. The required feeding time had to be >7 days. Patients with the ability to eat orally at admission and those with diabetes, gastrointestinal disease, or recent gastrointestinal surgery were excluded.

Intervention

Initially, all patients underwent CF. After achieving ≥80% of the nutrition target calories (25–30 $kcal \cdot kg^{-1} \cdot day^{-1}$) through CF, the patients were randomly assigned into the SF group or the CF group by opening an opaque, sealed envelope containing the patient's randomization assignment. The bottle containing enteral nutrients was covered with an opaque bag so the patients were unaware of their intervention. However, the investigators knew the group assignment. For patients in the SF group, the feeding/fasting time was reasonably determined according to the circadian rhythm of the human body and the physiological movement of digestive organs as laid out in traditional Chinese medicine theory. The total daily dosage of enteral nutrition was equally distributed to three time periods of 7 to 9 o'clock, 11 to 13 o'clock, and 17 to 19 o'clock. Enteral nutritional suspension in each time period was pumped at a uniform rate within 2 h by an enteral feeding pump. Patients in the CF group received CF at a constant velocity by an enteral feeding pump. Fingertip blood glucose values at five time points (6:00/11:00/15.00/21:00/1:00) were monitored and recorded for seven consecutive days after randomization. Meanwhile, enteral feeding intolerance was recorded by a researcher-made checklist including the data on diarrhea, abdominal distension, constipation, and gastric residual volume (GRV).

Outcome measures

Baseline characteristics of the patients were recorded on a researcher-made checklist, including age, sex, weight, body mass index, major diagnosis, Acute Physiology and Chronic Health Evaluation II scores at the beginning, mechanical ventilation support, average target calories, total glucose infusion, and insulin therapy.

The primary outcome was the average blood glucose (GluAve) value over 7 days. GV was the secondary outcome. GV was assessed by three indices: standard deviation of glucose (GluSD), coefficient of glucose variation (GluCV), and $Glucose_{max}$-$Glucose_{min}$. GluCV is GluSD divided by GluAve. In addition, the events of hypoglycemia (glucose <3.9 mmol/L) and hyperglycemia (glucose >11.1 mmol/L) were also recorded.

Enteral feeding intolerance was another secondary outcome. The researcher-made checklist was used to evaluate enteral feeding intolerance, including the incidents of diarrhea, abdominal distension, constipation, and GRV. If

these events occurred, enteral feeding intolerance was confirmed: (1) Diarrhea: the patient had three or more loose stools or continued to have loose stools within 24 h.[15,16] (2) Abdominal distension: obvious abdominal distension or intra-abdominal pressure ≥12 mmHg.[17] (3) Constipation: fewer than three bowel movements per week or exertion during defecation and hard stools.[18] (4) GRV ≥200 mL by ultrasonic monitoring was a sign of intolerance.[19] In the SF group, GRV was assessed 2 h after stopping the feeding pump (at 11:00/15:00/21:00). In the CF group, GRV was also assessed at these three time points (11:00/15:00/21:00). The duration of mechanical ventilation, length of stay in the ICU, and ICU mortality rate were also recorded.

Statistical analysis

Non-inferiority testing was adopted in this study. In CF, the blood glucose value was approximately 9 mmol/L, and the standard deviation was approximately 3. We speculated that the blood glucose value was also 9 mmol/L. Then, α was set at 0.05, $1-\beta$ was set at 0.8, the non-inferiority value was set to 2, and the sample size calculated by PASS 11.0 software (NCSS, LLC, Kaysville, UT, USA) was 28 in each group. Another six patients were needed to correct for an expected 10% drop out. For the primary parameter, average glucose value, we used a one-sided Wilcoxon rank-sum test with $P < 0.050$ considered significant for non-inferiority statistics.

Other statistical analyses were performed by SPSS software version 22.0 (SPSS, Inc., Chicago, IL, USA). The results are expressed as the median (interquartile range). The chi-square test or Fisher test was used for qualitative data, and the Mann-Whitney *U* test was used for quantitative data to determine differences between groups. In particular, a repeated measure one-way analysis of variance (ANOVA) was used to identify whether changes in glucose value variables across the time points were different between the two groups. These results were expressed as mean ± standard deviation. Bonferroni *post hoc* tests were performed to determine significant differences in glucose in the repeated measures ANOVA. *P* values < 0.050 were considered statistically significant.

Results

A total of 903 patients were assessed for eligibility in the study from March to December 2018, and 62 patients were finally enrolled [Figure 1]. Thirty-two patients were randomized to the SF group, and 30 patients were randomized to the CF group.

General and clinical characteristics

The baseline characteristics of the patients in the two groups are presented in Table 1, and there were no significant differences between the two groups ($P > 0.050$).

Primary and secondary outcomes

The average glucose level in SF was not higher than that in CF (8.8 [7.3–10.3] *vs.* 10.7 [9.1–12.1] mmol/L, $Z = -2.079$, *P* for non-inferiority = 0.019). There were differences in the GluCV between the two groups (24.5 [22.2–27.6]% *vs.* 18.9 [13.7–25.3]%, $Z = -2.480$, $P = 0.013$). However, there were no significant differences in glucose standard deviations or $Glucose_{max}$-$Glucose_{min}$ between the two groups (2.2 [1.6–3.1] *vs.* 2.3 [0.9–2.6] mmol/L, $Z = -0.691$, $P = 0.489$; 7.5 [6.1–10.9] *vs.* 8.7 [3.9–10.4] mmol/L, $Z = 0.000$, $P = 0.999$) [Table 2]. The

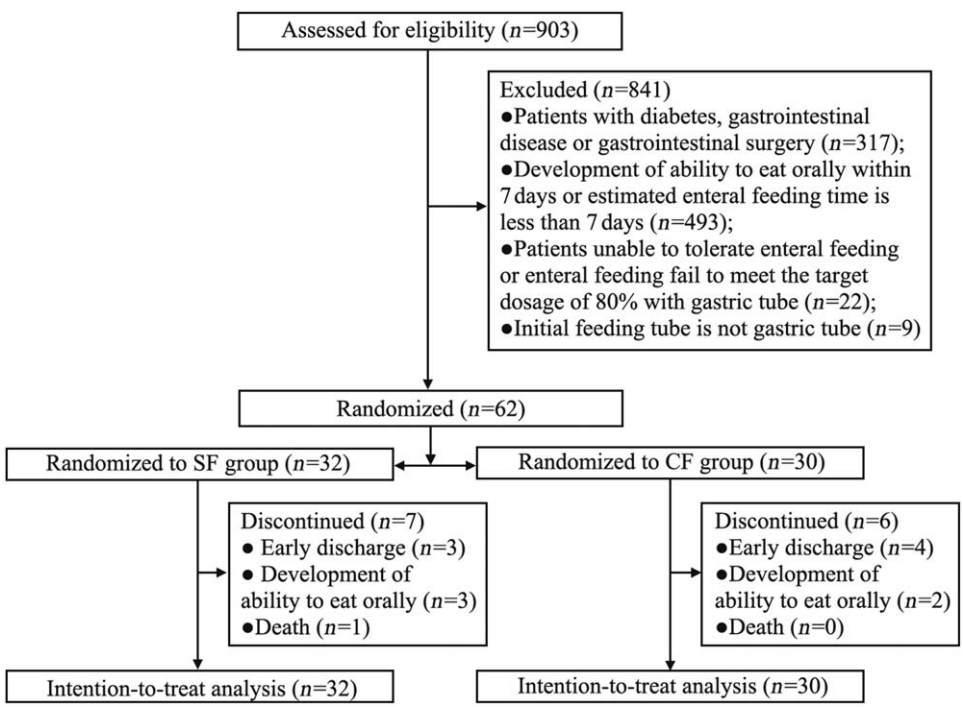

Figure 1: Flow diagram of the subjects. CF: Continuous feeding; SF: Sequential feeding.

Table 1: Comparison of general and clinical characteristics of the patients between the SF and CF groups.

Variables	SF group ($n=32$)	CF group ($n=30$)	Z/χ^2 value	P
Age (years)	66 (54–72)	55 (48–67)	−1.868	0.062
Gender (male/female)	17/15	19/11	0.663	0.416
Weight (kg)	65 (60–78)	65 (60–87)	−0.505	0.613
Body mass index (kg/m^2)	24 (20–26)	23 (21–24)	−1.347	0.178
APACHE II scores	19 (15–23)	16 (10–19)	−1.885	0.059
Mechanical ventilation support (yes/no)	26/6	28/2	2.012	0.258
Average target calories (kcal)	1671 (1403–1990)	1587 (1459–2072)	−0.249	0.804
Insulin therapy (yes/no)	8/24	10/20	0.522	0.470
Glucose infusion (yes/no)	22/10	18/12	0.518	0.472
Total glucose infusion (g)	100 (0–210)	30 (0–150)	−1.308	0.191
Major diagnosis				
Pneumonia	13/32	12/30	0.003	0.960
Brain diseases (stroke, hemorrhage, or infection)	10/32	9/30	0.011	0.915
Trauma	2/32	5/30	1.677	0.249
Cardiac arrest	1/32	2/30	0.422	0.607
Hepatobiliary infection	2/32	1/30	0.286	0.999
Others	4/32	1/30	1.755	0.355

Data are presented as median (interquartile range) or *n*/*N*. APACHE II scores: Acute Physiology and Chronic Health Evaluation II scores; CF: Continuous feeding; SF: Sequential feeding.

Table 2: Comparison of outcomes between the SF and CF groups.

Variables	SF group ($n=32$)	CF group ($n=30$)	Z/χ^2 value	P
GluAve (mmol/L)	8.8 (7.3–10.3)	10.7 (9.1–12.1)	−2.079	0.019*
GV				
GluSD (mmol/L)	2.2 (1.6–3.1)	2.3 (0.9–2.6)	−0.691	0.489
GluCV (%)	24.5 (22.2–27.6)	18.9 (13.7–25.3)	−2.480	0.013
Glu_{max}-Glu_{min} (mmol/L)	7.5 (6.1–10.9)	8.7 (3.9–10.4)	0.000	0.999
Incidence of feeding intolerance	4/32	2/30	0.603	0.672
Hyperglycemia (yes/no)	25/7	25/5	0.269	0.604
Hyperglycemia incidence of each patient (%)	11.8 (3.0–36.7)	38.4 (19.1–63.7)	−2.213	0.027
Mechanical ventilation days	10 (4–23)	17 (10–28)	−2.166	0.030
Lengths of stay in ICU (days)	22 (12–27)	25 (12–31)	−0.784	0.433
Mortality in ICU	2/32	2/30	0.004	0.999

Data are presented as median (interquartile range) or *n*/*N*. GV was assessed by three indices: GluSD, GluCV, and Glu_{max}-Glu_{min}. *A one-sided Mann-Whitney *U* test for non-inferiority statistics. CF: Continuous feeding; GluAve: Average glucose; GluCV: Coefficient of glucose variation; GluSD: Standard deviation of glucose; GV: Glycemic variability; SF: Sequential feeding.

results of the repeated-measures ANOVA indicated that there was a significant effect of time on glucose levels ($F=22.302$, $P<0.001$), and there was an interaction between time and intervention for glucose levels ($F=5.638$, $P=0.001$). At the 9:00, 15:00, and 21:00 time points, there were no significant differences in glucose between the two groups ($P>0.050$). At the 6:00 and 1:00 time points, the average glucose value in the SF group was lower than that in the CF group (6.7 ± 2.3 *vs.* 8.1 ± 2.8 mmol/L, $t=-3.436$, $P=0.001$; 8.1 ± 1.5 *vs.* 10.5 ± 2.7 mmol/L, $t=-4.331$, $P<0.001$) [Table 3]. Moreover, hypoglycemia (glucose <3.9 mmol/L) was not found in either group. However, hyperglycemia incidence of each patient was more common in the CF group than that in the SF group (38.4 [19.1–63.7]% *vs.* 11.8 [3.0–36.7]%, $Z=-2.213$, $P=0.027$). The incidence of insulin therapy was not significantly different between the groups (8/32 *vs.* 10/30, $\chi^2=0.522$, $P=0.470$).

The mechanical ventilation days in the SF group were shorter than those in the CF group (10 [4–23] *vs.* 17 [10–28], $Z=-2.166$, $P=0.030$). Moreover, no significant differences in the incidence of feeding intolerance during the 7 days, the length of stay in the ICU or mortality in the ICU were found ($P>0.050$).

Discussion

In the present study, the average glucose level in SF was not higher than that in CF. In addition, hyperglycemia incidence was higher in the CF group than that in the SF group. There was no increase in feeding intolerance in SF.

A consensus has been reached on the importance of nutritional support for critically ill patients. However, the choice of enteral nutrition feeding method for ICU patients

Table 3: Comparison of average blood glucose between the SF and CF groups at five time points.

Variables	SF group ($n = 32$)	CF group ($n = 30$)	t value	P
6:00 GluAve (mmol/L)	6.7 ± 2.3	8.1 ± 2.8	−3.436	0.001
11:00 GluAve (mmol/L)	9.8 ± 3.7	10.6 ± 2.3	−1.138	0.260
15:00 GluAve (mmol/L)	10.1 ± 2.9	10.9 ± 2.5	−1.011	0.316
21:00 GluAve (mmol/L)	10.2 ± 2.7	10.4 ± 2.4	−0.259	0.780
1:00 GluAve (mmol/L)	8.1 ± 1.5	10.5 ± 2.7	−4.331	<0.001

Data are presented as mean ± standard deviation. CF: Continuous feeding; GluAve: Average glucose; SF: Sequential feeding.

is still controversial. CF was thought to be better tolerated by critically ill patients with gastrointestinal dysfunction, allowing for easy insulin control and controlling for a limited absorptive gut surface area.[5] However, when patients achieve 80% of the nutrition target volume, their gastrointestinal function is almost restored. At this time point, it is unclear whether CF is necessary. Moreover, continuous nutritional delivery alters circadian rhythms of intestinal hormones and post-prandial rhythms of ghrelin and insulin release in response to nutrition.[20] Circadian misalignment is detrimental to metabolism.[21,22] The selection of the time points in SF is based on the theory of the human body clock in traditional Chinese medicine, and we thought this SF was also beneficial for ICU patients.

As a new feeding mode, the safety of SF should be concerned. Critically ill patients usually develop high glucose values, which are associated with adverse outcomes.[13] This study showed that the average glucose level of the SF group was not higher than that of the CF group. Blood glucose levels in subjects in the SF group at 6:00 and 1:00 were lower than those in the CF group. In addition, the incidence of hyperglycemia in the SF group was less than that in the CF group, and no cases of hypoglycemia occurred in the SF group.

The avoidance of glucose variability causing negative outcomes is a priority for patients in the ICU.[23] It is the belief of many clinicians that continuous rather than intermittent feeding helps to reduce this variability. However, in a recent study of 50 critically ill patients comparing bolus feeding given via a percutaneous endoscopic gastrostomy tube with CF, no difference in glucose variability or insulin utilization was found.[5] Our study also suggested that there were no significant differences in glucose standard deviations and $Glucose_{max}$-$Glucose_{min}$ between the two groups. However, we also found that the GluCV in the SF group was higher than that in the CF group. Previous studies have shown that glucose variability affects the prognosis of critically ill patients,[23] but when patients can tolerate 80% enteral nutrition, this often indicates that their condition has stabilized, and a reasonable fluctuation of blood glucose may be beneficial to patients since it was shown that reasonable glucose variability causes infusion fluctuation, which is beneficial for protein synthesis.[24] In addition, previous studies on glucose variability all used CF, and the influence of glucose variability in CF and SF may be different. In this study, a difference in mortality was not found. Additional studies are needed to confirm the effects of glucose variability in SF.

Feeding intolerance is very common in patients in the ICU, especially in terms of delayed gastric emptying. It has been shown that both the rate and extent of nutrient absorption are impaired, even during post-pyloric feeding.[25] A study has yet to be performed in critically ill patients, and intermittent feeding may increase gut motility by increasing superior mesenteric artery blood flow and enhancing cholecystokinin and peptide YY concentrations.[20] Similar to other studies,[3,4] our study also suggested no significant differences in the incidence of feeding intolerance between the two feeding modes.

CF may have the following advantages[25]: better GRV management in some populations, better blood sugar control in early stages of a critical illness, it is less labor-intensive for nursing staff and there is a wider choice of enteral feeds. On the other hand, intermittent feeding has the following advantages[25]: enhancing muscle protein synthesis, ability to "catch up" on missed feeds, a reduction in diarrhea, and freedom from the pump during rehabilitation and other procedures. SF as applied in this study may integrate the advantages of CF and intermittent feeding. CF is used at the initial stage when the gastrointestinal function is impaired, and intermittent feeding, which supports the circadian rhythm of the human body, is used after almost complete recovery of gastrointestinal function. This study demonstrated that the average glucose and enteral feeding intolerance of patients in the ICU were similar in both SF and CF. So, SF may be as safe as CF for patients in the ICU.

There were some limitations to this study. First, many patients were excluded for various reasons, such as diabetes and gastrointestinal diseases, and further studies are needed to determine whether the results of this study are suitable for such patients. Second, the observation period is over 7 days, and whether the same conclusion can be reached in a shorter period, such as 3 days, requires further study.

In this non-inferiority study, the GluAve value of critically ill patients with SF was not higher than that of critically ill patients with CF. Compared with CF, hyperglycemia was less frequent in SF. There was no significant difference in the incidence of feeding intolerance between SF and CF. Therefore, SF may be as safe as CF for critically ill patients.

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Conflicts of interest

None.

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