Effect of Different Feeding Methods on Gastrointestinal Function in Critical Patients (DFM-GFC): Study Protocol For a Randomized Controlled Trial

Bojun Zheng
the second affiliated hospital of guangzhou Chinese medicine
Jian Li
guangdong provincial hospital of Chinese Medicine
Yi Yu
the second affiliated hospital of guangzhou university of Chinese medicine
Aijing Deng
the second affiliated hospital of guangzhou university of Chinese medicine
Honglian Ouyang
guangdong provincial hospital of Chinese medicine
Huang Xin
Guangdong Provincial Academy of Traditional Chinese Medicine
Hong Chen
guangdong provincial hospital of Chinese medicine
Guang Yang (yangguang@gzucm.edu.cn)
the second affiliated hospital of guangzhou Chinese medicine https://orcid.org/0000-0001-9140-9159

Study protocol

Keywords: critical illness, enteral nutrition, feeding method, gastrointestinal disorders

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Abstract

Background: Enteral nutrition is a major pathway of nutrition for patients requiring critical care. However, whether intermittent or continuous feeding is better is not yet known clearly, especially after nasogastric enteral nutrition via gastric tube. Therefore, this randomized controlled clinical study was designed to observe the effects of different methods on critically ill patients.

Methods: The different feeding method on gastrointestinal function of critical patients (DFM-GFC) was a randomized, single-blind, clinical study assessing the effects of three feeding methods on critically ill patients. A total of 90 critical patients were equally randomized to three groups: continuous feeding, cycling feeding, and intermittent feeding. The patients were pumped with gastrointestinal nutrition preparation via gastric tube in 24 h or in 16 h via intermittent pump. The primary outcome is the mean duration that reached to the caloric goal in every group. The secondary outcome included the rate of onset of gastric residua, abdominal pressure, the rate of onset pneumonia, and the proportion of individuals achieving the caloric goal. Also, the length of intensive care unit (ICU) stay and mortality rate at 28 days post-enrollment was evaluated.

Discussion: This study observes the effects of different feeding methods on parameters, such as energy target and gastrointestinal motility in critically ill patients, in order to improve the prognosis of, quality of life and reduce the case fatality rate.

Trial registration: ClinicalTrials.gov ID: NCT04224883. Registered on January 9, 2020.

Introduction

Background and rationale {6a}

The majority of the critical patients in the intensive care unit (ICU) require analgesia, sedation, and mechanical ventilation as they are unable to feed on their own and need enteral nutrition (EN). Compared to parenteral nutrition (PN), EN is under intensive focus. In the case of critically ill patients, several guidelines recommend initiating EN as soon as possible after ICU admission if patients are able to eat[1]. These guidelines state that EN preparation is pumped by nasogastric tube or nasointestinal tube; however, the specific protocol is not known.

EN can be administered by numerous methods. Three common feeding methods include continuous, intermittent, and cyclic feeding. For example, during continuous feeding, an electric infusion feeding pump delivers EN at a constant hourly rate: 24 h/day. During cyclic feeding, a feeding pump administers EN in <24 h. During intermittent feeding, EN is administered using a feeding pump over 20–60 min every 4–6 h [2].

Some studies suggested that continuous feeding is well-tolerated in patients but can lead to blocked catheters and poor patient mobility because our gastrointestinal tract is constantly digesting food with no

time to empty the same. In contrast to continuous feeding, bolus feeding is a physiological mode of delivery. In replicating normal patterns of feeding, bolus delivery allows the phased supply of hypertonic nutrient loads into the jejunum, which reduces the metabolic demand on the small intestine and prevents excessive accumulation of jejunal fluid[3-4]; however, it causes complications, such as vomiting, aspiration, and fluctuations in blood sugar[5-6]. The subsequent 6 h in cyclic feeding enhance a patient's appetite and/or restore gastric acidity, but only a few studies have focused on cyclic feeding. Intermittent feeding at standard intervals allow greater patient mobility and is considered a physiological method with respect to the cephalic phase of digestion and gut homeostasis[7].Hitherto, whether the pump should be continuous or intermittent and the specific plan for pumping is controversial. The critical care nutrition expert panel identified the need for a continuous vs. intermittent feeding trial as one of the "top10" priority studies to be carried out in the next decade[8]. Moreover, cycling feeding methods are less studied in China.

Objectives {7}

Although the pumping time of intermittent feeding is less than that of continuous pumping, it would not prolong the target feeding time, and would reduce the incidence of complications, such as gastric residual and aspiration pneumonia.

Trial design {8}

This is a prospective randomized controlled study.

Methods: Participants, Interventions And Outcomes

Study setting {9}

Three separate cohorts of patients admitted to the ICU of Guangdong Hospital of Traditional Chinese Medicine, Guangzhou, China.

Eligibility criteria {10}

Inclusion criteria

Participants (1) aged 18–80 years; (2) with Acute Physiology and Chronic Health Evaluation (APACHE)-II ≥15[9]; (3) in whom EN can be used after evaluation; (4) are expected to be in the ICU for >48 h.

Exclusion criteria

Participants (1) required to fast clinically, such as patients with digestive tract perforation, bleeding, or gastrointestinal tract surgery; (2) allergic to EN preparations; (3) in the early stage of sepsis (within a week) and associated with hemodynamic instability; (4) unwilling to cipate in the trial or cannot cooperate with the treatment; (5) who are pregnant and lactating; (6) with unstable hemodynamics.

Who will take informed consent? {26a}

The patients or their family member/authorizer who fulfilled the study requirements were offered a consent form consisting of the details, such as the name of the study, registered information, research background, how the study was to be conducted, what the participants should do in the study, inclusion/exclusion criteria, treatment plans and obligations, putative drug-related side effects, and expenses during participation. The patients' personal medical data was maintained confidential. Participation in this study was voluntary, and other treatment options were offered to the patients who did not participate or drop out in this study. Informed consent was obtained from the patients to utilize their personal and medical information in this study. To protect the privacy of the subjects, data processing was performed anonymously, and informed consent was obtained from each patient or statutory agent before initiation of the clinical trial.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

No applicated

Interventions

Explanation for the choice of comparators {6b}

For EN[10], the current guidelines recommend the use of pumping, which is often compared to manual infusion[11]. Continuous feeding, intermittent feeding and cyclic feeding are three common feeding methods.Some studies[12-14] have demonstrated that continuous pumping does not improve blood sugar levels, stomach retention, and the occurrence of ventilator-associated pneumonia.

Intervention description {11a}

Patients were randomized into three arms: continuous feeding group, cycling feeding group, and intermittent feeding group. In the continuous group, an electric infusion feeding pump delivers EN at a constant hourly rate, 24 h/day. The critical patients randomized to the cycling feeding group received EN preparation for 16 h by continuous pumping through the stomach tube every day. The initial pumping speed of two groups was 50 mL/h, and the gastric residual volumes (GRV) was checked every 4 h. If it can be tolerated, the velocity of the pumping can be increased by half of the original speed. If it is not tolerable, the speed of the pumping is reduced by half of the original speed. GRV<500 mL was considered as a marker of adequate tolerance. Feeding intolerance was defined as GRV>500 mL. The critical patients randomized to the intermittent feeding group were administered EN preparation by four meals every day (08:00, 12:00,18:00, 22:00); each meal was pumped within 60 min through the stomach tube. In the intermittent group, the daily amount of feeding was divided into four meals, and each meal was pumped through the stomach tube within 60 min. EN preparation pumping scheme was as follows: the initial pumping speed was 250 mL/h, and the GRV was checked before each intermittent feeding. If it can be tolerated, the velocity of the pumping was increased by half of the original speed. If it was not tolerable, the speed of the pumping was reduced by half of the original speed. All feeding was started within 24 h

of admission to the ICU. EN suspension ((SP, Peptisorb), Nutricia Pharmaceuticals (Wuxi, Jiangsu, China) Co. Ltd) was selected for the preparing EN. The calorie content was 1 kcal/mL and thermal nitrogen ratio was 133:1. Each bottle contains 500 mL nutrition preparation consisting of 61.5 g carbohydrate, 20.0 g protein, and 19.45 g fat (Wuxi). The treatment course was 5 days (Fig. 1).

Criteria for discontinuing or modifying allocated interventions {11b}

Withdrawal/trial discontinuation/drop-out criteria

Participants (1) who cannot tolerate the nutrition preparation, resulting in diarrhea, severe abdominal distension, and other complications; (2) or family members who request automatic withdrawal at any time.

Strategies to improve adherence to interventions {11c}

Ouyang Honglian supervised the compliance of pumping mode by checking the execution of doctors' orders. The clinical Specimen department of Guangdong Academy of Chinese Medicine carries out unified management and preservation of the collected blood specimens.

Relevant concomitant care permitted or prohibited during the trial {11d}

Relevant concomitant care is prohibited during the trial.

Provisions for post-trial care {30}

Adverse medical event (AEs) of the intervention measures in this study are rare. Any AEs that occurs in subjects during observation of a clinical study might be related to the drug of interest. The AE report form was completed during the trial. The time of occurrence, severity, duration, actions taken, and outcomes of AEs were recorded, and those occurring during follow-up were reported to the sponsor in a timely manner. Furthermore, serious AEs were reported simultaneously to the adverse drug reaction (ADR) monitoring center of the local authority within 24 h and the sponsor. The study team will give priority to unpaid examination and treatment according to the regulations of the ETHICS Committee.

Outcomes {12}

Primary outcome

The primary outcome is the mean duration (h) required to achieve the caloric goal in every group. The caloric goal of 25 kcal/kg (ideal body weight) for caloric need was calculated by a single nutritionist. The duration was the first 5 days after intervention.

Secondary outcome

Secondary outcomes included the following: (1) The rate of onset of gastric residual (%) (defined as volume >500 mL) among three groups. (2) Abdominal pressure (mmHg) was measured through the

indirect bladder pressure; first in the supine position, emptying the bladder urine, second pouring 50 mL saline into the balloon catheter to the pubic symphysis as the base point, keeping the piezometric tube perpendicular to the ground to obtain indirect abdominal pressure. (3) The rate of onset of pneumonia was evaluated in each group (%). It was defined by two of the following clinical criteria: fever (>38.3 °C) or hypothermia (≤36.0 °C); leukocytosis (>10×10^9 cells/L) or leukopenia (≤4×10^9 cells/L); purulent tracheal aspirate or sputum. These factors were associated with the appearance of a new infiltrate or changes in the existing infiltrate on the chest X-ray.[15] (4) The proportion (%) of individuals who achieved the caloric goal. The caloric goals using 25 kcal/kg (ideal body weight) for caloric need were calculated by a single nutritionist. (5) Motilin levels before and 5 days after intervention. (6)The length of the ICU stay (in days) up to 12 weeks. (7) The ICU mortality rate (%) at 28 days after intervention and survival analysis up to 12 weeks.

Participant timeline {13}

Sample size {14}

The sample size was calculated based on the incidence of gastric retention and aspiration size (P=0.05, P=-0.20, respectively). Compared to the continuous group, Patients in the intermittent and cycling groups did not reduce the percentage of patients who met the target calories, which was 80 percent. A standard deviation of the outcome variable of 70% power and a significance level of 0.05 (two-sided) was set, ratio of patients in continuous group and in the intermittent, cycling groups with continuous group is 0.5. So a sample size of 26 patients in each group was required; however, the total sample size was 84. Based on the sample size in previous studies, and assuming that the withdrawal rate is <8–10% [16], we expected that 30 patients to be enrolled in each arm and that the total sample size was at least 90.

Recruitment {15}

Recruitment advertisements will be posted in the department to facilitate recruitment.Guang Yang or Yi Yu is responsible for talking to the patient or his statutory agent and obtaining informed consent.

Assignment of interventions: allocation

Sequence generation {16a}

A random number table generated by SPSS 20.0 software (IBM Co., Armonk, NY, USA), using the randomization method, was employed to assign the participants to each group in a ratio of 1:1:1. Patients were enrolled in allocated accordance with the sequence of admission to ICU.

Concealment mechanism {16b}

Center randomization/Envelopes containing random sequences and groups are sealed and opaque.

Implementation {16c}

Jian Li will generate the allocation sequence, Guang Yang will enrol participants and assign participants to interventions.

Assignment of interventions: Blinding

Who will be blinded {17a}

Since this study was a comparative assessment of treatment modalities, blinding was not feasible. Masking was applied to the assessment team, data manager, and statistician related to the participant treatment arm allocation and to the treatment team for the baseline and follow-up assessments.

Procedure for unblinding if needed {17b}

No

Data collection and management

Plans for assessment and collection of outcomes {18a}

The Second Affiliated Hospital of Guangzhou University of Chinese Medicine was in charge of data management and statistical analysis in this study. The statistical analysts were not involved in clinical observation. Study personnel will undergo training sessions on data collection and are individually tested on data entry as well as outcomes assessments before trial initiation. Study data is collected and managed using SPSS 20.0.

Plans to promote participant retention and complete follow-up {18b}

Follow-up or telephone follow-up was conducted 28 days after the intervention.

Data management {19}

An independent data safety monitoring board (DSMB) will receive trial data from the biostatistician and choose to continue the study as planned, change the study protocol, or stop the trial early for harm. Double data entry is carried out by special persons and reported to DSMB.

Confidentiality {27}

The participants' medical records were maintained at the hospital, and the investigator, research authority, and the ethics committee were allowed access to this information. Any public report on the results of this study did not disclose the participants' personal identities. Every effort was made to protect the privacy of participants' personal medical data, according to the law. Personal and medical information was kept confidential in a safe and reliable place. At any time, the participants may request access to their personal information (such as address and contact information) and may modify the same if necessary.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

The clinical Specimen department of Guangdong Academy of Chinese Medicine carries out unified management and preservation of the collected blood specimens. Motilin levels were determined by elisa in the laboratory of critical care Medicine of Guangdong Academy of Chinese Medicine.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

All statistical analyses were performed using SPSS 20.0 software. Measurement data were expressed as mean ± standard deviation. Normality test and homogeneity test of variance were also performed. In case of normal distribution and homogeneity of variance, a t-test was conducted, otherwise a non-parametric test was used. If the measurement data conforms to normal distribution, then independent sample t-test was applied between the two groups and one-way analysis of variance (ANOVA) was utilized between three groups. In the case of non-normal distribution, the two groups were compared using the Mann–Whitney U test, while Kruskal–Wallis test was utilized between three groups. The enumeration data between two and three groups were compared using chi-square/crosstab statistical analysis and expressed as frequency constituent ratio (%). $P<0.05$ indicated statistical significance.

Interim analyses {21b}

The trial can be prematurely paused or closed by the DSMB in order to evaluate safety information from the study, or if there is evidence of harm in the study. Principal investigator(PI) can access to these interim result.

Methods for additional analyses (e.g. subgroup analyses) {20b}

Not Applicable

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Patients who died or were lost to follow-up will have their observation time censored at the time of death or date of last contact. For patients with early withdrawal and lost to follow-up, intentional analysis was used. For all primary and secondary endpoints, we will consider a repeated measurement approach based on mixed models which contain both fixed effects (eg, Abdominal pressure measurement technique) and random effects (eg, patient). These models are likelihood-based approaches in the presence of ignorable missing data (ie, missing at random) and are a proper way to accommodate information on a patient with outcomes, even when such a patient's profile is incomplete. For second endpoint (6), cumulative proportion surviving curves according Kaplan-Meier will be obtained for each group and compared with

the method of log-rank test. In order to explore the group effect on the time to event of composite outcome adjusting for baseline covariates, the Cox regression model will be fitted.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

Granting full access to the protocol is intended, but participant-level dataset and statistical code is not intended

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

The coordinating centre, steering committee and endpoint adjudication committee 's responsibilities shall be assumed by the Ethics Committee of Guangdong Hospital of Chinese Medicine, reviewing the data for at least half a year.

Composition of the data monitoring committee, its role and reporting structure {21a}

Monitoring will be performed by an independent data safety monitoring board (DSMB) consisting of three members with expertise in critical care, clinical trial methodology, and biostatistics. The DSMB will receive trial data from the biostatistician and choose to continue the study as planned, change the study protocol, or stop the trial early for harm. The DSMB will submit The experimental data to The Ethics Committee of Guangdong Hospital of Traditional Chinese Medicine for review at least once every 6 months. Related data from each DSMB meeting will be retained in a secured file for inspection by regulatory authorities.

Adverse event reporting and harms {22}

Any adverse medical event (AEs) that occurs in subjects during observation of a clinical study might be related to the interventions of interest. The AE report form was completed during the trial. The time of occurrence, severity, duration, actions taken, and outcomes of AEs were recorded, and those occurring during follow-up were reported to the sponsor in a timely manner. Furthermore, serious AEs were reported simultaneously to the adverse drug reaction (ADR) monitoring center of the local authority within 24 h and the sponsor.

Frequency and plans for auditing trial conduct {23}

auditing trial conduct is once a year. The process will be independent from investigators and the sponsor.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

If the research plan needs to be modified, it shall provide relevant explanatory materials and application to the ethical Committee, and the modification can only be made after approval.

Dissemination plans {31a}

Access to the final dataset will be retained with the study investigators. Compensation for the trial, including harm, is not intended. Results of the trial are intended for publication in a peer-reviewed journal by the authors, and assistance of professional writers is not expected.

Discussion

Although the guidelines stated that EN should be given by pumping, there is no agreement on whether continuous pumping should be applied or the duration of pumping. The DFM-GFC study on three common nasal feeding methods, such as continuous pumping feeding method, intermittent pumping feeding method, and circulating pumping feeding method, achieved the same goal of heat entrapment, reduced the gastrointestinal complications, improved the gastric retention, and reduced the occurrence of aspiration and aspiration pneumonia. Although the incidence of complications did not decline significantly, the cost of treatment was lower if the intermittent pumping and circulating pumping feeding method was accomplished in less time than the continuous pumping feeding method.

Although the guidelines for EN are constantly being updated, nutritional preparations are also being improved. However, the duration of EN[17], the use of nutritional additives (such as fish oil), the selection of nutritional preparations[18], and the pathway of EN, are under intensive focus. Furthermore, for EN[10], the current guidelines recommend the use of pumping, which is often compared to manual infusion[11]. Some studies[12–14] have demonstrated that continuous pumping does not improve blood sugar levels, stomach retention, and the occurrence of ventilator-associated pneumonia.

According to the people's physiology and habit, it is necessary to rest during the inter-meal time, and three meals/day is not required. Eating several meals a day is largely conditioned by material conditions and social behavior. In ancient Greece, no one ate three meals a day, only two, according to Homer's literature. Nonetheless, the physiologically appropriate number of meals per day for humans is an enigma. During sleep, the peristalsis of the gastrointestinal tract is slowed, and the secretion of the digestive juices is reduced. Some studies[19] demonstrated that there is no difference in the amount of water in the small intestine and the amount of hormones secreted by the small intestine using continuous pumping and bolus through a gastric tube in healthy individuals.

A previous study[20] found that intermittent bolus feeding enhances muscle protein synthesis to a greater extent than continuous feeding by eliciting a pulsatile pattern of amino acid- and insulin-induced translation initiation. Moreover, it increases the difficulty in moving or turning[21]. Continuous pumping is not a physiological condition and can lead to tube clogging[22]. Although intermittent feeding can be cost-effective for the patients, would continuous pumping be optimal in terms of treatment effectiveness and complications? So, this study compared the effects of continuous feeding, cycling feeding, and intermittent feeding in critically ill patients, including complications such as vomiting, diarrhea, and the length of stay in the ICU and increase in the hospitalization costs due to aspiration pneumonia. Thus, this

study would recommend the best treatment for EN in critically ill patients and a basis for the development of EN guidelines.

Trial status

Enrollment don't start. Recruitment will start in July 2020 and is expected to conclude June 2021. Target enrollment for the study is 90 subjects

Abbreviations

ICU: intensive care unit; EN:enteral nutrition; PN: parenteral nutrition;APACHE-II:Acute Physiology and Chronic Health Evaluation-II; GRV: gastric residual volumes; AE: Adverse medical event; ADR: adverse drug reaction;DSMB: data safety monitoring board.

Declarations

Ethics approval and consent to participate {24}

This trial was conducted in accordance with the Helsinki Declaration and Chinese Good Clinical Practice[23]. The relevant regulations and protocols were approved by the Medical Ethics Committee of the Second Affiliated Hospital of Guangzhou University of Chinese Medicine (No. Z2016-049-01). To protect the privacy of the subjects, data processing was performed anonymously, and informed consent was obtained from each patient or statutory agent before initiation of the clinical trial.. Changes to the protocol were submitted to the ethics committee for review. Informed consent was obtained from all participants in the trial.

Consent for publication {32}

Consent forms for the trial include consent for publication of results in peerreviewed journals.

Availability of data and materials {29}

Data results from this randomized controlled study are unavailable at the time of publication. Individual participant data available upon request..

Competing interests {28}

The authors declare that they have no competing interests.

Funding {4}

The DFM-GFC study is supported by the Guangdong Provincial Bureau of Chinese Medicine. The funding agency has no role in the development of the study design, collection, analysis, interpretation of data, manuscript development, or the decision to submit the manuscript for publication.

Authors' contributions {31b}

Study concept and design: Guang Yang. Acquisition of data: Honglian Ouyang and Hong Chen. Analysis of data: Aijing Deng. Drafting of manuscript: Yi Yu and Bojun Zheng. Detection of biochemical indicators: Xin Huang. Funding: Honglian Ouyang Study supervision: Jian Li. All authors read and approved the final manuscript.

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Authors' information (optional)

Jian Li:lijian426@126.com; Yi Yu: 1191922959@qq.com; Bojun Zheng: 517256767@qq.com; Aijing Deng: tallaileen@163.com; Honglian Ouyang: oyhlwjx@126.com; Xin Huang: huangxin373@163.com; Hong Chen:16883700@qq.com; Guang Yang: yangguang@gzucm.edu.cn

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Figures

			STUDY PERIOD						
	Enrolment	Allocation	Post-allocation						Close-out
TIMEPOINT**	$-t_1$	0	1day	2day	3day	4day	5day	28day	12week
ENROLMENT:									
Eligibility screen	X								
Informed consent	X								
Allocation		X							
INTERVENTIONS:									
continuous feeding			←	—	—	—	→		
cycling feeding			←	—	—	—	→		
intermittent feeding			←	—	—	—	→		
ASSESSMENTS:									
*SOFA, APACHE-II, liver and renal function**		X			X		X		
caloric intake, evaluating goal reached			X	X	X	X	X		
gastric residual, Abdominal pressure, onset of pneumonia			X	X	X	X	X		
Motilin levels		X			X		X		
The length of the ICU stay									X
mortality rate								X	X

* Liver function includes alanine aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin and albumin.Renal function includes blood creatinine and urea.

Figure 1

Schedule of enrolment, interventions, and assessments.