

Early Enteral Permissive Underfeeding in Critically Ill Young Adults with Traumatic Brain Injury: A Single-Blind Randomized Controlled Pilot Trial

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Abstract

Background and Objectives: There is no consensus on optimal initial energy requirements for critically ill patients. The present study aimed to compare the clinical outcomes of early enteral permissive underfeeding (EPU) with those of early enteral standard feeding (EESF) in critically ill patients with traumatic brain injury (TBI).

Materials and Methods: In this single-blind, randomized, controlled pilot trial, 60 young adults with TBI were randomly assigned to either EESF or EPU groups (initiation energy goal: 100% vs. 30% of estimated energy requirements, respectively). Enteral feeding was administered during 24-48 hours of intensive care unit admission. Patients receiving EPU were prescribed to achieve full energy requirements by day seven of the intervention.

Results: The EPU group demonstrated improved glycemic control (205.6 ± 68 vs. 137.4 ± 59 mg/dL, $P=0.02$), reduced duration of hospital stay (57.5 ± 29 vs. 70.9 ± 24 days, $P=0.08$) and shorter duration of mechanical ventilation (20.2 ± 11 vs. 26.4 ± 9 days, $P=0.04$). Gastrointestinal complications were more frequent in the EESF group (3.5 ± 2 vs. 1.4 ± 3 days, $P=0.001$). There were no differences between the EESF and EPU groups in terms of 28-day mortality rate (3.8% vs. 10.7%, RR: 0.33; 95% CI: 0.03, 3.42; $P=0.61$).

Conclusion: EPU may be associated with beneficial effects on gastrointestinal toleration and glycemic control in young TBI patients, which might contribute to improved clinical outcomes in this population; however, further investigations are required on this issue.

Trial registration: This trial was registered at Iranian Registry of Clinical Trials (www.irct.ir) as IRCT201201128709N1.

Introduction

Traumatic brain injury (TBI) represents a major public health concern given its high incidence and mortality rates [1–2]. TBI patients are often hypermetabolic and hypercatabolic [2–3]; these patients are usually unable to fulfill their increased nutritional requirements by oral feeding alone, even if oral feeding is possible [4]. Still, TBI patients are prone to develop malnutrition and other complications [2, 4–5]. Provision of adequate nutritional support is associated with reduced risk of developing malnutrition and improved clinical outcomes in critically ill patients [6–7]; however, there is a scarcity of robust evidence to declare the optimal energy requirements of critically ill patients [8], particularly in those with head trauma [9–10].

Traditionally, the aim of the nutritional support was provision of the desired level of energy and protein to suppress the deleterious effects of undernutrition originating during the early days of admission to intensive care unit (ICU) [7, 11]. On the other hand, overfeeding and excess calorie intake is considered to be detrimental [7], perhaps due to the adverse impact of accelerated oxygen radical production on wasting fuel and mitochondria [10]. Accordingly, in the recent years, a trend towards short period of

caloric restriction during the first few days of admission to ICU was propounded for nutritional management of critically ill patients [12].

Observational studies investigating varied doses of enteral feeding yielded inconsistent results [3–7]. Rubinson et al. found that low caloric intake (< 25% of the average daily recommended calorie) was associated with nosocomial bloodstream infections in patients admitted to ICUs [8]. The study by Krishnan et al. indicated that moderate caloric intake (33%-65% of the recommended American College of Chest Physicians targets) was associated with reduced mechanical ventilation duration, length of ICU stay, and hospital mortality rate [10]. Dickerson et al. demonstrated that hypocaloric enteral tube feeding (< 20 kcal/kg vs. ≥ 20 kcal/kg) in critically ill obese patients shortened length of ICU stay ($P < 0.03$), reduced duration of antibiotic therapy ($P < 0.03$), and a trend towards curtailed mechanical ventilation duration ($P = 0.09$) [11].

Ibrahim et al. studied early versus late enteral feeding of mechanically ventilated patients [12]. The late group received a lower level of calorie (629 ± 575 kcal vs. $2,370 \pm 2,000$ kcal, $P < 0.001$) and had fewer incidence of ventilator-associated pneumonia, less *Clostridium difficile*-induced diarrhea, as well as shorter ICU and hospital length of stay compared with the early feeding group [12].

Two cluster-randomized, controlled trials comparing high enteral nutritional delivery with the routine care in critically ill patients showed no reduction in the rate of mortality in the group receiving higher enteral nutrition [8, 9].

Two randomized, controlled trials performed on patients with acute lung injury or acute respiratory failure revealed that initial trophic enteral feeding (15–25% of the estimated caloric requirements with no protein supplementation) for up to six days reduced gastrointestinal tolerance; however, it did not improve ventilator-free days or 60-day mortality rate [13, 14]. These outcomes were similar to those with standard enteral feeding.

A Randomized Controlled Trial (RCT) of 240 general medical-surgical mechanically-ventilated patients compared the efficacy of a moderate hypocaloric (60–70% of the estimated caloric requirements) versus standard caloric (90–100%) intake with maintenance of full targeted protein intake in two groups. Lower caloric intake was associated with reduced in-hospital mortality, which was a secondary end point [25].

Caloric restriction is shown to extend life span in several species [12–14], promote mammalian cell survival [15], and improve longevity biomarkers in humans [16] possibly through its effect on metabolic, hormonal, and inflammatory pathways [12, 14, 16]. Additionally, along with the provision of adequate calorie and protein requirements, early onset of nutritional support is of crucial importance in nutritional management of TBI patients. Currently, the Brain Trauma foundation proposed a level II recommendation, stating that TBI patients should receive their target energy and nutritional requirements by day seven post-injury [27–28]; likewise, the American Society for Parenteral and Enteral Nutrition (ASPEN) and the Society of Critical Care Medicine recommended initiating early enteral nutrition within the first 24–72 hours post-injury and increasing the administration rate to reach the established peak within the next 2–3

days [28–29]. Accordingly, some evidence support the beneficial effects of reaching target energy requirements within five-seven days after injury on morbidity [25, 30] and mortality [31–32] rates of TBI patients.

The constituents of optimal energy dose for patients with TBI during the early days post-injury are still unclear [2, 5, 9–10, 15, 28]. In this study, therefore, we aimed to examine the effects of EEPU versus EESF on clinical outcomes in critically ill patients with TBI.

Materials And Methods

Study design

This single-center, randomized, controlled pilot trial was conducted on 16 trauma and neurosurgical patients admitted to ICU of Shahid Kamyab Hospital, a tertiary-care hospital affiliated to Mashhad University of Medical Sciences, Mashhad, Iran, during November 2011-June 2012. This project was approved by the ethics committee of Mashhad University of Medical Sciences and was registered with code 900382.

The inclusion criteria included being in the age range of 18–65 years and admitted to ICU with TBI (with grades 2 or 3 of Hunt-Hess classification and diffuse axonal injury, not subjected to surgery) as well as meeting the indications of enteral tube feeding and were expected to stay in the ICU more than 96 hours. The exclusion criteria are presented in Table 1. Written informed consent was obtained before enrollment from all the patients or their legal representatives.

Interventions

The enrolled patients were randomly assigned to early enteral permissive underfeeding (EEPU) and early enteral standard feeding (EESF) groups, using sealed numbered envelopes.

Intensive care management of the patients with TBI was offered in accordance to brain injury classification, institutional treatment protocol implementation, and daily clinical observations.

Enteral feeding was commenced by providing 100% of the calculated energy requirements from day one in the EESF group and by 30% of the calculated energy requirements during the first 48 hours of enrollment in the EEPU group, followed by 60–75% of the standard caloric requirements during the second 48 hours of the intervention. The subsequent volume of enteral feeds was increased by 100 mL until 100% of the calculated energy requirements were achieved. Standard caloric requirements were estimated by the dietitians according to the American College of Chest Physicians equation [35]. Enteral feeding was administered using the commercially available standard and high protein formulas (Enterameal, Karen Pharma Co., Tehran, Iran). The type of formula (standard formula: 0.9 kcal/mL, 35 g protein/L or high protein formula: 1.08 kcal/mL, 48 g protein/L) was determined by the dietitians as long as it satisfied the predefined goal caloric requirements for each group.

A goal protein intake of 0.8–1.5 g/kg per day was calculated for the EEPU and EESF groups based on patient conditions and discretion of the treating physician [13, 29, 36]. To prevent protein malnutrition in the EEPU group, supplementary protein (Resource Beneprotein; Nestle Healthcare Nutrition Inc, Minneapolis, MN) was added to the enteral formula to maintain the required protein intake.

The patients' abdomen was assessed regularly at least four times a day by the nursing staff and once daily by a member of the nutrition support team. Gastric residual volume (GRV) was checked every three hours. In case GRVs exceeded 200 mL in two sequential feeding intervals, the feeding was suspended; gastric residual was returned into the stomach and rechecked three hours later until the residual volume was less than 200 mL to resume the feedings. For patients with persistent elevated gastric residuals and abdominal distension or vomiting, prokinetic therapy with either metoclopramide or erythromycin was initiated [29].

Data collection

At baseline, demographic data including age, gender, height, and mid-arm circumference (based on tape measurement), weight (using bed scale, Seca 984 bed scale, Seca Deutschland, Germany) were recorded along with ICU admission diagnosis (subtypes of traumatic brain injury), severity of illness (based on Acute Physiology and Chronic Health Evaluation [APACHE II] score) [34], mechanical ventilation, inclusion blood glucose concentration, serum creatinine, bilirubin, and platelet count, vasopressor therapy (defined as the use of any vasopressor infusion except for dopamine, 5 µg/kg per minute), partial pressure of oxygen to the fraction of inspired oxygen ratio ($\text{PaO}_2:\text{FiO}_2$), and Glasgow Coma Scale.

Nutritional data including energy and protein intakes and the amount and consistency of bowel movements were recorded on a daily basis. The energy plans were continued based on the latest estimation of energy requirements for each participant after seven days.

Clinical outcome measures including ICU mortality, 28-day all-cause mortality, length of hospital stay, and duration of mechanical ventilation were recorded, as well. Additionally, the incidence of hyperglycemia (defined as blood glucose concentration of ≥ 126 mg/dL or 7 mmol/L), as well as the number of days that patients experiencing gastrointestinal intolerance (defined as either diarrhea associated with clostridium difficile infection or at least two episodes of elevated gastric residual volumes [(GRVs) > 200 mL] and the number of nil per os [NPO] days due to gastrointestinal complications) were recorded for all the patients. We also recorded the use of the selected medications during ICU stay.

Blood samples were collected in the afternoon of days 0 (the time of ICU admission), 7, and 14. Regular follow-up examinations were performed for all the patients until discharge, unless the patient tolerated oral feeding, had an officially approved do-not-resuscitate order, or became brain dead after randomization. The outcome data were documented for these patients, despite the intervention was ceased.

Statistical analysis

The study variables were assessed based on intention-to-treat analyses. The collected data were analysed using SPSS, version 11.5. The data were evaluated for normality homoscedasticity for all the independent variables. All P-values were two-tailed, and statistical significance was defined as $P < 0.05$. Continuous data were displayed as mean \pm SD, and categorical data were expressed as percentage of its relevant patient group.

To compare baseline characteristics and outcome variables t-test was used for continuous variables, whereas for categorical variables Chi-square test was performed. One-way repeated- analysis of variance was run to assess and compare the serial data between the groups, followed by post hoc analysis by Tukey's HSD test to evaluate the differences across the time points. For mortality data, relative risk (RR) and 95% confidence intervals (CIs) were calculated. Log-rank test was employed to compare Kaplan-Meier survival curves to determine probability of survival.

Results

Patients

Out of the 546 assessed patients, 60 patients were included in the study. The enrolled patients were randomly assigned to either EESF or EEPU groups (Fig. 1). Baseline characteristics of the patients are presented in Table 2; indicating no statistically significant differences between the two study groups.

Interventions

Enteral nutrition administration began 19.8 ± 13 hours and 25.2 ± 12 hours after ICU admission for the EESF and EEPU groups, respectively ($P = 0.11$; Table 2). The majority of patients (56 out of 60; 93.3%) received high protein formula except for two patients in the EESF group and another two in the EEPU group, who received the alternate standard formula.

Calculated energy requirements on day zero showed no statistically significant differences between the two study groups (Table 3); however, the study energy goal was set lower for the patients in the EEPU group during the first week of the intervention, whereas the patients in the EESF group were prescribed to receive 100% of the calculated caloric requirements from the first day after admission.

During the first week of intervention, the patients in the EEPU group received significantly lower level of calories than the EESF group (985.5 ± 149 vs. 1448.6 ± 353 kcal/day, $P < .0001$; Table 3). Nevertheless, energy intake in the EESF group was lower than prescribed (77.2%) due to intermittent discontinuation of feeding due to gastrointestinal complications including high residuals, abdominal distension, vomiting, and diarrhea, which eventually resulted in lower commutative energy intake compared with the prescribed study energy goal in this group. On the other hand, due to the gradual increase in caloric intake in the EEPU group during the first week of study, the patients were able to achieve a better caloric intake and experienced fewer episodes of gastrointestinal intolerance.

The two groups were not significantly different in terms of mean protein intake during the first week of the study (58.5 ± 17 vs. 52.6 ± 16 g/day, $P = 0.20$; Table 3). All the patients were prescribed to receive their calculated caloric requirements in the second week of the study. As anticipated, both study groups reached a plateau of caloric intake during the second week; accordingly, the means of energy and protein intake were similar in the EESF and EEPU groups during this time (1469.2 ± 500 vs. 1429.1 ± 598 kcal/day, $P = 0.80$ and 65.2 ± 5 vs. 64.1 ± 3 g/day, $P = 0.62$; Tables 3 and 4). Nonetheless, implementing various medical procedures led to temporary interruption in the feeding of patients, which resulted in lower actual caloric intake compared to what was prescribed; similar phenomenon was noted in previous studies [16, 38–39].

Outcomes

The patients in the EEPU group experienced shorter length of hospital stay (57.5 ± 29 vs. 70.9 ± 24 days, $P = 0.08$; Table 4) and significantly fewer days on mechanical ventilation (20.2 ± 11 vs. 26.4 ± 9 days, $P = 0.04$) than the patients in the EESF group (Table 4). However, no statistically significant difference was observed in terms of 28-day all-cause mortality rate between patients in the EESF and the EEPU groups (3.8% vs. 10.7% , RR: 0.33; 95% CI: 0.32, 3.42; $P = 0.61$; Table 4). ICU mortality was 13.3% in the EESF group and 6.7% in the EEPU group (RR: 2.00; 95% CI: 0.36, 12.76; $P = 0.67$). Kaplan-Meier plots of the survival estimates showed no significant differences in the possibility of 28-day survival between the two groups (log-rank test, $P = 0.341$).

In the EEPU group, blood glucose control improved compared to the EESF group; a lower mean glucose concentration was observed during week one (137.4 ± 59 vs. 205.6 ± 68 mg/dL, $P = 0.02$) and week two after initiating enteral nutrition (123.3 ± 34 vs. 199.5 ± 66 mg/dL, $P = 0.03$; Table 4) in the EEPU group. The results of One-way repeated measures ANOVA showed no statistically significant differences in the means of serial blood glucose concentrations between the EESF ($P = 0.06$) and EEPU ($P = 0.26$) groups over the entire study period.

Patients in the EESF group experienced more episodes of persistent elevated gastric residual volumes (GRV > 200 mL), and showed higher incidence of diarrhea associated with clostridium difficile infection. Overall, the occurrence of gastrointestinal intolerance was more common in the EESF rather than the EEPU group (3.5 ± 2 vs. 1.4 ± 3 days, $P = 0.001$). Similarly, the EESF group experienced more NPO days during gastrointestinal symptoms (1.1 ± 1 vs. 0.6 ± 1 days, $P = 0.06$; Table 4).

Discussion

The main outcomes of our pilot study were providing TBI patients with early enteral feeding, short-term (seven days) caloric restriction associated with fewer episodes of gastrointestinal intolerance, improved glycemic control, shorter duration of mechanical ventilation, and a trend towards reduced length of hospital stay compared to the early standard enteral feeding.

Previous studies investigating the association between the level of caloric intake and clinical outcomes in critically ill patients rendered conflicting results [6, 9, 13–14, 16–17, 23–25, 40–42], possibly due to heterogeneity in their design, patient population, feeding strategies and formulas, as well as diversity in the route of delivery and feeding rate and timing.

Although some similarities were present between the design of our study and that of the previous ones [13, 25, 41], to the best of our knowledge, this study was the first attempt to compare the effect of short-term EEPU versus EESF in young non-malnourished adults with TBI admitted to ICU; besides, enteral feeding of patients in the EEPU group was initiated at a rate of 30% of calculated energy requirements, and gradually advanced until the patients received 100% of the calculated energy requirements by the end of week one after initiating the intervention.

Our findings did not demonstrate a significant difference in 28-day and ICU mortality rates between the two groups, which could be due to various reasons. Caloric intakes of both study groups were below what was planned, particularly during the first week in the EESF group (achieved: 77.2% vs. planned: 100%). Difficulty to achieve the nutritional targets in ICU, specifically in the intervention studies planning to reach target calorie goals was well documented by former studies [9, 13, 25, 38, 41].

In our study, extended episodes and frequencies of gastrointestinal intolerance including slow gastric emptying, elevated gastric residual volumes, diarrhea, distention, and cramps resulted in lower energy intake, particularly in the EESF group compared to the EEPU group. Accordingly, a trend towards a higher number of NPO days was recorded in the EESF group compared with the EEPU group (1.1 ± 1 vs. 0.6 ± 1).

Results of some studies suggested higher risk of *Clostridium difficile*-associated diarrhea with use of specific pharmacological interventions such as proton-pump inhibitors and certain classes of antibiotics [43–45]. However, we believe that a significant difference in the use of drugs was not present between our study groups, as the percentage of patients receiving antibiotics (22% vs. 23%) and acid suppressants (25% vs. 21%) in the EEPU and EESF groups were alike.

Similarly, Rice et al. [41] and Ibrahim et al. [13] proposed that aggressive early enteral nutrition was associated with increased gastrointestinal complications in critically ill patients with acute respiratory failure. On the other hand, the gradual increase in caloric intake in the EEPU group possibly diminished our chance to provide patients with sufficient caloric restriction to observe a significant difference in the mortality rate, which is in accordance with several previous observational studies [14, 17].

Furthermore, the small sample size possibly undermined the likelihood of observing significant treatment effects, as it was based on the anticipated treatment effects resulting from observational studies [46]. Contrary to the commonly used outcome measure of 28-day all-cause mortality in randomized controlled trials, long-term outcome measures such as 90-day and 180-day mortality rates might detect the effect of calorie restriction on the survival and mortality rate of critically ill patients more efficiently. In this regard, results of larger RCTs with long-term outcome measures and follow-ups in different clinical settings such as PermiT Trial [10] are awaited.

Our data showed that the patients in the EEPU group had fewer days on mechanical ventilation and less days of hospitalization. The results of clinical trials and observational studies still lack conclusive evidence on this issue. In the pioneering cohort study of 48 critically ill surgical patients, Villet et al. [24] demonstrated that cumulative energy deficit is associated with prolonged duration of mechanical ventilation and ICU stay.

Discordantly, Dvir et al. [23] propounded that maximum negative energy balance does not have a significant effect on mechanical ventilation duration as well as length of ICU and hospital stay. Conflictingly, results of a retrospective analysis on 40 trauma and surgical obese patients by Dickerson et al.¹⁶ demonstrated that the patients in hypocaloric group had fewer days on mechanical ventilation compared to the patients in full-caloric group (16.6 ± 11.7 vs. 27.4 ± 17.3 days). Similar to our findings, Ibrahim et al. [13], pointed out that mechanically ventilated medical patients in hypocaloric group had a reduced incidence of ventilator-associated pneumonia (30.7% vs. 49.3%, $P = 0.020$) and fewer days of hospital stay (16.7 ± 12.5 vs. 22.9 ± 19.7 days).

Most recently, the results of EDEN study, a multicenter trial conducted by the National Heart, Lung and Blood Institute on acute respiratory distress syndrome, showed that patients with acute lung injury who received full enteral feeding suffered from gastrointestinal intolerance more than trophic feeding group [47].

Our findings showed that progressive advancement of caloric intake in TBI patients resulted in more efficient glycemic control and a concomitant decrease in the incidence of hyperglycemia. As with similar previous studies, Mc Cowen et al. [48] reported no significant differences in the incidence of hyperglycemia in critically ill patients who received either the isocaloric total parenteral nutrition (TPN) regimen (25 kcal/kg, 1.5 g/kg protein) or the hypocaloric TPN regimen (1000 kcal/day, 70 g of protein); however, the study was limited due to fixed energy intake in the latter group regardless of the patients' weight and the difference in TPN formulation between the two groups. The results of EDEN randomized trial [47] delineated that the mean plasma glucose value was lower in the trophic-feeding group during the first six days of enteral nutrition compared with full-feeding group.

The present study should be highlighted through its strengths and limitations. Its strengths include blinded design (RCT), random assignment of the enrolled patients using concealed envelopes, and well-balanced distribution of patients in the two study groups. All our patients were healthy young adults who had a minimum history of chronic diseases or malnutrition before admission to ICU. Follow-up examinations were completed for all the patients.

Our study had several limitations; it was a single-center study, mainly conducted in the trauma ICU and therefore, we cannot be sure that our findings are generalizable to other patient populations. Unfortunately, we did not achieve the predicted energy requirements, particularly in the EESF group. According to the consensus guideline recommendations [29, 49–50] and the practical routine in our ICU, energy requirements were calculated using the American College of Chest Physicians equations rather

than the calorimetric methods; hence, we cannot be confident that our estimated energy requirements are based on the actual metabolic demands of all our patients.

Given these limitations, further study is warranted to optimize nutritional strategies and routes of delivery and to ascertain that all patients receive energy requirements based on the actual metabolic demands as well as their entire calculated protein requirements. By undertaking a large, randomized, controlled, multicenter trial, the quality of these data could be promoted.

In conclusion, the strategy of early enteral permissive underfeeding for up to seven days may be associated with favorable effects on certain clinical outcomes such as fewer gastrointestinal complications, improved glycemic control, and reduced length of mechanical ventilation when compared with standard early enteral feeding.

Conclusion

EPU may be associated with beneficial effects on gastrointestinal toleration and glycemic control in young TBI patients, which might contribute to improved clinical outcomes in this population; however, further investigations are required on this issue.

Abbreviations

RCT: Randomized clinical trial; EPU: Early enteral permissive underfeeding; EESF: Early enteral standard; TBI: Traumatic brain injury; TPN: Total parenteral nutrition; ICU: Intensive care unit.

Declarations

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Authors' contributions

MK, AN, MN, HA, FS and MRE designed the research. MK, NP, MM, AN, BB, and FS performed the trial, MN, AN, HA, MM, and NP analyzed and interpreted the data and drafted the manuscript. All of the authors read and approved the final manuscript.

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Availability of data and materials

Patients' private information in our study is not publicly available because of lack of agreement for disclosing individual data in public but are available from the corresponding and first author on reasonable requests and can be uploaded to the journal site as raw data whenever requested.

Ethics approval and consent to participate

This project was approved by the ethics committee of Mashhad University of Medical Sciences and was registered with code 900382, and informed consent was obtained from all patients or their first-degree relatives to participate in the study.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1
Exclusion Criteria

Age < 18 or ≥ 66 years
Brain death or expectations of death within 48 hours of ICU admission
Transferred from another ICU or another hospital
Enrollment in competing trial
Malnourishment (classified by the ICU nutrition support team at the time of hospitalization)
Received artificial (enteral or parenteral) nutritional support before admission to the ICU
Pregnancy, lactation
Any of the following conditions Renal dysfunction (defined as serum creatinine > 1.5 mg/dL) Heart failure Hepatic dysfunction (defined as serum bilirubin > 3 mg/dL) Cholestasis, Cirrhosis or Hepatitis Pancreatitis Diabetes Congenital or autoimmune diseases Malignancy Indications of parenteral nutrition or oral feeding
ICU, intensive care unit.

Table 2
Baseline Characteristics of EESF and EEPU Groups of Patients

Characteristics	EESF Group ^a (n = 30)	EEPU Group ^a (n = 30)	P Value ^b
Age (y)	35.9 ± 16	34.8 ± 15	.94
Female sex [n (%)]	2 (6.7)	5 (16.7)	.42
Intensive care unit diagnosis [n (%)]			.44
SAH	4 (13.3)	7 (23.3)	
SDH	6 (20)	8 (26.7)	
Contusion	7 (23.3)	3 (10.0)	
IVH	5 (16.7)	2 (6.7)	
SAH + SDH	4 (13.3)	7 (23.3)	
EDH	4 (13.3)	3 (10.0)	
Weight (kg)	71.6 ± 12	69.0 ± 8	.35
Ideal body weight (kg)	69.4 ± 6	68.5 ± 7	.62
BMI (kg/m ²)	25.0 ± 3	24.1 ± 2	.28
MAC (cm)	29.4 ± 3	28.4 ± 3	.27
APACHEII score	18.4 ± 3	19.1 ± 4	.52
EEPU, early enteral permissive underfeeding; EESF, early enteral standard feeding; SAH, subarachnoid hemorrhage; SDH, subdural hemorrhage; IVH, intraventricular hemorrhage; EDH, epidural hemorrhage; BMI, body mass index; MAC, mid-arm circumference; APACHE II, Acute Physiology and Chronic Health Evaluation II.			
^a Values are presented as mean ± SD; ^b a t test was used for continuous variables, and a chi-square test was used for categorical variables.			

Table 2
Baseline Characteristics EESF and EEPU Groups of Patients (Cont.)

Characteristics	EESF Group ^a (n = 30)	EEPU Group ^a (n = 30)	P Value ^b
Mechanical ventilation [n (%)]	25 (83.3)	22 (73.3)	.35
PaO ₂ :FiO ₂	141 ± 95	147 ± 100	.59
Vasopressor [n (%)]	17 (56.7)	16 (53.3)	.80
Inclusion blood glucose (mg/dL) ^c	155.9 ± 32	154.7 ± 53	.91
Creatinine (mg/dL)	0.89 ± 0.3	0.89 ± 0.4	.72
Bilirubin (mg/dL)	1.74 ± 76	1.60 ± 74	.51
Platelets (10 ⁹ /L)	259.3 ± 49	243.2 ± 55	.24
Glasgow coma scale (GCS)	7.2 ± 1	7.0 ± 1	.68
Enteral feedings initiated (hr)	19.8 ± 13	25.2 ± 12	.11
Calculated energy requirement (kcal)	1873.8 ± 162	1850.4 ± 207	.63
EEPU, early enteral permissive underfeeding; EESF, early enteral standard feeding; GCS, Glasgow Coma Scale.			
^a Values are presented as mean ± SD; ^b a t test was used for continuous variables, and a chi-square test was used for categorical variables; ^c to convert to conventional units in mmol/L, multiple by 0.0555 for glucose, 88.4 for creatinine and 17.1 for bilirubin.			

Table 3

Summary of Energy and Protein Intakes of EESF and EEPU Groups during the Study Period

Variable	EESF Group ^a (n = 30)	EEPU Group ^a (n = 30)	P Value ^b
Calculated energy requirement (kcal/day)	1873.8 ± 162	1850.4 ± 207	.63
Study energy goal (kcal/day)			
Week 1	1873.8 ± 162	1145.7 ± 132	< .0001
Week 2	1873.8 ± 162	1850.4 ± 207	.63
Average energy intake (kcal/day)			
Week 1	1448.6 ± 353	985.5 ± 149	< .0001
Week 2	1469.2 ± 500	1429.1 ± 598	.80
% Energy intake/Calculated energy requirement			
Week 1	77.2 ± 14	53.5 ± 12	< .0001
Week 2	78.0 ± 19	77.8 ± 20	.97
EEPU, early enteral permissive underfeeding; EESF, early enteral standard feeding.			
^a Values are presented as mean ± SD; ^b a t test was used for continuous variables, and a chi-square test was used for categorical variables.			

Table 3

Summary of Energy and Protein Intakes of EESF and EEPU Groups during the Study Period (Cont.)

Variable	EESF Group ^a (n = 30)	EEPU Group ^a (n = 30)	P Value ^b
Calculated protein requirement (g/day)	83.3 ± 7	82.2 ± 9	.63
Average protein intake (kcal/day)			
Week 1	64.4 ± 3	61.6 ± 4	.24
Week 2	65.2 ± 5	64.1 ± 3	.67
% Protein intake/requirement			
Week 1	77.2 ± 7	74.7 ± 9	.48
Week 2	78.5 ± 9	78.0 ± 8	.85
EEPU, early enteral permissive underfeeding; EESF, early enteral standard feeding.			
^a Values are presented as mean ± SD; ^b a t test was used for continuous variables, and a chi-square test was used for categorical variables.			

Table 4
Clinical Outcomes in the EESF and EEPU Groups

Variable	EESF Group ^a (n = 30)	EEPU Group ^a (n = 30)	P Value ^b
ICU mortality [n (%)]	4/30 (13.3)	2/30 (6.7)	.67 ^c
28-d Mortality [n (%)]	1/26 (3.8)	3/28 (10.7)	.61 ^d
Hospital LOS (day)	70.9 ± 24	57.5 ± 29	.08
Mechanical ventilation duration (day)	26.4 ± 9	20.2 ± 11	.04
Average blood glucose concentration (mg/dL)			
Day 0	155.9 ± 32	154.7 ± 53	.91
Day 7	205.6 ± 68	137.4 ± 59	.02
Day 14	199.5 ± 66	123.3 ± 34	.03
Gastrointestinal complications (day) ^e	3.5 ± 2	1.4 ± 3	.001
NPO days (day) ^f	1.1 ± 1	.6 ± 1	.06
EEPU, early enteral permissive underfeeding; EESF, early enteral standard feeding; ICU, intensive care unit; LOS, length of stay; NPO, nothing by mouth.			
^a Values are presented as mean ± SD; ^b a chi-square test was used for categorical variables; ^c RR (95% CI): 2.00 (.36, 12.76); ^d RR (95% CI): .33 (.03, 3.42); ^e Diarrhea associated with Clostridium difficile infection or persistent elevated gastric residual volumes; ^f Number of NPO days associated with gastrointestinal intolerance.			

Figures

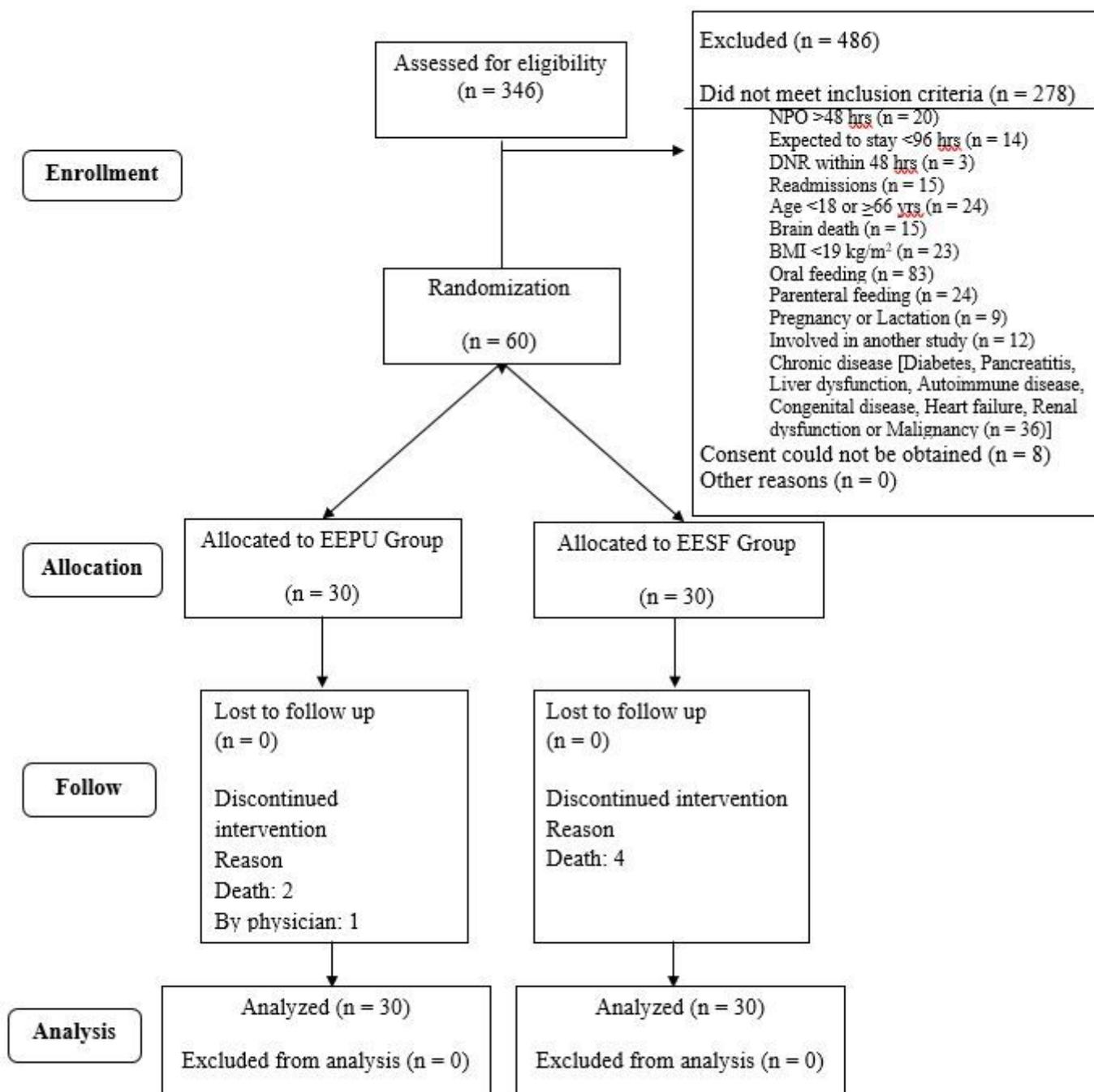


Figure 1

Flow diagram of patients in the study. All randomly assigned patients were included in the analysis according to intention-to-treat principle. Values are indicated as the number of patients. EEPU, early enteral permissive underfeeding; EESF, early enteral standard feeding; NPO, nothing by mouth; DNR, do not resuscitate; BMI: body mass index.

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