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High-protein delivery in mechanically ventilated patients: A study protocol for a randomized trial

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ABSTRACT:

Background: Critically ill patients are at risk of malnutrition; thus, optimal nutrition delivery is a key treatment for better outcomes. Inadequate energy and protein intake increase rate of hospital-acquired infection, duration of mechanical ventilation and mortality. However, there is no clear consensus regarding optimal protein dose in mechanically ventilated patients. In this study, we aim to compare between the effect of high and usual protein delivery on clinical outcomes in this patient group.

Methods: This is a single-centered, open-labelled, parallel-group, randomized controlled study conducting in medical, surgical and trauma intensive care units (ICU) at a tertiary university hospital in Bangkok, Thailand. We plan to enroll 240 adult mechanically ventilated patients who are expected to require ventilator support for at least 3 days. The intervention group will be prescribed high protein dose (at least 1.5 g/kg/day) throughout ICU stay since day 4 until a maximum of 28 days, whereas the control group will be prescribed usual protein dose (1-1.3 g/kg/day). Nutrition is provided by enteral or parenteral route or both. The primary outcome is ventilator-free days at 28 days. The main secondary outcomes include the temporal change in muscle mass and SOFA score, rate of nosocomial infection and 28-day mortality.

Conclusion: The robust evidence whether delivering high protein in critically ill patients improves outcome is lacking. This randomized trial will examine the consequence of high protein delivery in ICU population.

Keywords: Critically ill, Intensive care units, Mechanically ventilated patients, Nutrition, High protein

INTRODUCTION

Critically ill patients admitted in the intensive care unit (ICU) for more than 48 hours are at high risk for malnutrition [1]. Optimal provision of nutrition enhances patients' recovery from critical illness and minimizes rate of complications [2]. However, the majority of ICU patients obtain inadequate nutrition due to various obstacles, thereby increasing risk of undernutrition [3] which contributes to increased muscle mass losses, ICU-acquired weakness [4] and the rate of hospital-acquired infection [5].

A previous prospective observational study in mechanically ventilated patients showed that an adequacy of both caloric and protein intake was associated with decreased 28-day mortality, while achieving only caloric target without adequate protein was not associated with decreased mortality [6]. Likewise, another observational trial demonstrated the survival benefit of increased caloric and protein delivery [7]. These findings emphasize the importance of an adequacy of both calories and protein in ICU patients.

The optimal amount of protein intake in mechanically ventilated patients is still inconclusive because of lack of solid evidence. Most previous studies are observational showing the benefit of more protein intake. Looijaard et al. [8] showed that protein delivery (> 1.2 g/kg/day) in patients with low skeletal muscle mass was associated with decreased 60-day mortality. Moreover, an additional daily protein intake for 30 g was associated with increased ventilator-free days (VFDs) [9]. Zusman et al. [10] demonstrated that a reduction in 60-day mortality was observed in patients who received protein at least 1.3 g/kg/day, and every additional 1 g of daily protein intake was associated with 1% decrease in mortality.

Recent large randomized controlled trials (RCTs) showed various results. EAT-ICU study by Allingstrup et al. [11] compared between early goal-directed nutrition guided by indirect calorimetry and urine urea nitrogen versus standard nutrition, showing that the physical quality of life at 6 months was not different. Additionally, a feasibility RCT by Chapple et al. [12] in 116 mechanically ventilated adults revealed that high protein enteral nutrition (EN) was not superior to usual protein delivery (1.52 vs 0.99 g/kg/d) with similar energy delivery in terms of 90-day mortality. Nevertheless, the RCT by Nakamura et al. [13] demonstrated the clinical benefit of using higher protein target at 1.8 g/kg/day by mitigating the loss of thigh muscle at day 10.

Concerning the safety of high protein dosing, aforementioned studies reported no sign of harm [12, 13,14]. Furthermore, delivery of 2.0-2.5 g/kg/day of protein was found to be safe in most critically ill patients [15]. However, excessive protein intake may result in elevation of blood urea or ammonia in patients with severe renal or liver insufficiency [16]. As the potential benefits and low risk of harm, we propose a single-centered RCT to examine the effects of high protein dose compared with usual protein dose in this patient group.

KEY MESSAGES:

- Existing evidence demonstrate unclear results regarding the optimal amount of protein intake in critically ill population.
- We propose a single-centered randomized controlled study to investigate the effects of high protein delivery in mechanically ventilated patients.
- We hypothesize that the prescription of high protein dose at least 1.5 g/kg/d among this patient group is superior to standard protein dose by increasing the number of ventilator-free days at day 28.

OBJECTIVES

The study primarily aimed to investigate the effect of high protein dosing (≥1.5 g/kg/day) versus usual standard protein dosing (1.2-1.3 g/kg/day) on 28-day VFDs in adult mechanically ventilated patients.

MATERIALS AND METHODS

This single-centered, open-labelled RCT is conducted in medical, surgical and trauma ICUs at a tertiary, university hospital in Bangkok, Thailand. The study protocol is approved by the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (certificate of approval no. Si 853/2021). Written informed consents from patients or next of kin are required prior to enrollment of participants. The study is performed in accordance with the Declaration of Helsinki.

Study population

Inclusion criteria

- Adult patients (age > 18 years)
- Admitted to the ICUs no later than 3 days
- Mechanically ventilated
- Expected to require ventilator support at least 3 days

Exclusion criteria

- Severe liver impairment: Child Pugh score ≥ 7, hepatic encephalopathy grade 2 or above, liver failure
- Acute kidney injury stage 3 without dialysis or chronic kidney disease stage 3b or above without dialysis
- Hemodynamic instability despite appropriate resuscitation, or escalating vasopressor doses (norepinephrine ≥ 0.2 mcg/kg/min, adrenaline ≥ 0.1 mcg/kg/min, dopamine ≥ 10 mcg/kg/min)
- Pregnancy
- End of life situation or palliative care
- Moribund or high probability of death

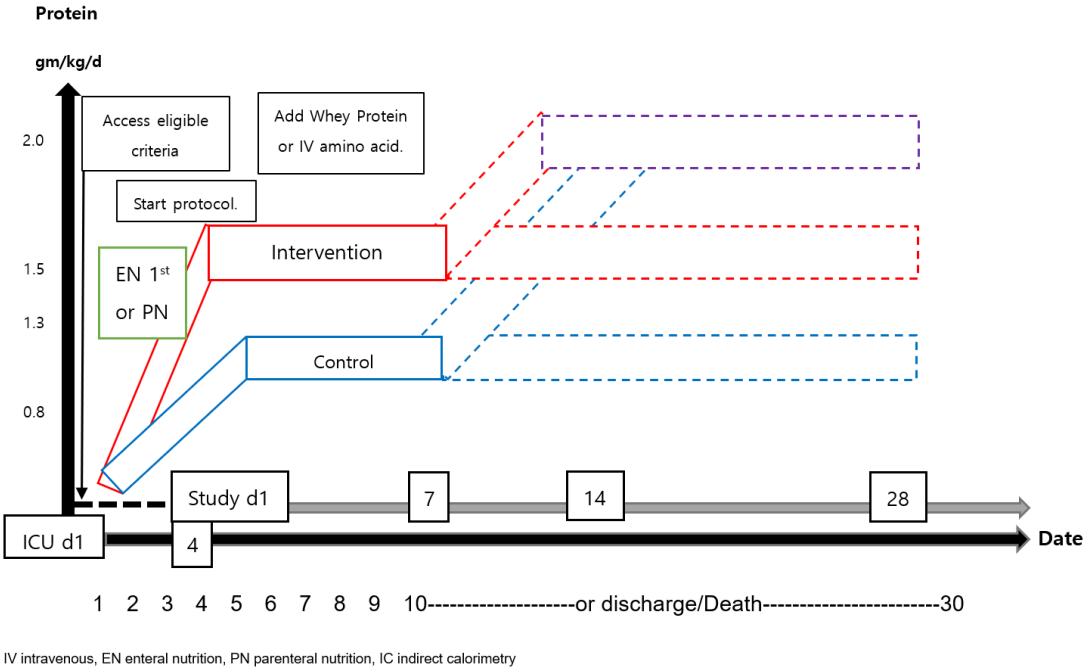

Figure 1. Graphic protocol of nutritional supplement in each group.

Randomization

After enrollment, patients are randomly assigned in a 1:1 ratio into either the intervention or the control arm. Central randomization is used and allocation sequence is concealed and computer-generated using block of 4 randomization.

Intervention

The intervention group will be prescribed high protein dose (at least 1.5 g/kg/day) throughout ICU stay since day 4 until a maximum of 28 days, whereas the control group will be prescribed usual protein dose. Target calories can be derived from either simple weight-based equation (20-25 kcal/kg/day during ICU day 4-7 and 25-30 kcal/kg/day since ICU day 8 onwards) or indirect calorimetry if available.

Enteral nutrition (EN) or parenteral nutrition (PN) or both can be delivered as clinically indicated. In order to achieving target dose of protein, protein supplements including enteral whey protein isolates or parenteral amino acid solutions are allowed to add. Protein doses can be adjusted every 5-7 days as a result of nitrogen balance study in order to maintain positive nitrogen balance. If BUN level is above 60 mg/dL, we reduce the protein intake by 0.1 g/kg/day. The graphical protocol of nutritional supplement is shown in Figure 1.

Data collection

Baseline demographic and laboratory data including admission diagnosis and severity of disease (APACHE II and SOFA score) will be recorded. Nutritional status is evaluated by using Subjective Global Assessment (SGA), Nutrition Alert Form (NAF) score and bioelectrical impedance vector analysis (BIVA). Urine urea nitrogen 24 hours is also collected.

The types and amounts of calories and protein received are recorded daily including gastrointestinal symptoms. SOFA score, nutritional status and nitrogen balance study will be evaluated every week. At day 28, survival status and VFDs were assessed, including the physical component summary (PCS) score of SF-36, length of mechanical ventilation, ICU and hospital stay and rate of nosocomial infection. Data collecting during study period is shown in Table 1 and the timeline of the study is shown in Table 2.

Outcome measures

The primary outcome is the VFDs at day 28 which are basically defined as duration that the patient is liberated from mechanical ventilation during 28 days since inclusion to the study. VFDs are zero if the patient dies within 28 days or they are mechanically ventilated for the whole 28 days. The secondary outcomes include the change in muscle mass evaluated by BIVA, the change in SOFA score, PCS score of SF-36 at day 28, rate of nosocomial infection, length of ICU and hospital stay and 28-day mortality. A visual definition of VFDs is shown in Figure 2.

Adverse events

The current clinical guideline suggests 1.2-2 g/kg/day of protein [17]. We consider the protein dose in our study is within acceptable range. However, excessive protein supply may result in hyperammonemia or uremia especially in patients with hepatic or kidney dysfunction without dialysis [15]). Blood urea nitrogen (BUN) and ammonium level will be monitored in these patients who develop deterioration of consciousness.

DATA ANALYSIS PLAN

Sample size

Previous study in our medical ICU showed that VFDs among mechanically ventilated patients were 9.7±10 days [18]. We assume that the clinically significant difference is 4 days. With 80% power, a type I error rate of 5%, and add-on 20% of populations, a sample of 120 patients per group is required by the nQuery Advisor program.

Table 1. Data collecting during study period.

ICU Day	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Up to +7d or ICU discharge, Death**						
	Enrolment				**Allocation**	**Post-allocation**								**D/C**	**Death**
Study Day					1	2	3	4	5	6	7	14	28	….	….
Enrolment															
Eligibility screen		X													
Inform consent		X													
Allocation					X										
Study group															
Control: Protein# 0.8-1.2 *Calory 20-25 or IC*					X	X	X	X	X	X					
Calory 25-30 or IC											X	X	X		
Intervention: Protein ≥ 1.5 *Calory 20-25 or IC*					X	X	X	X	X	X					
Calory 25-30 or IC											X	X	X		
Parameter															
Baseline variables, Lab(CBC, blood chemistry,Prealbumin,Lactate,CRP)	X	→	→	→	→	→	→	→	→	→	X	X	X		X
Ventilator data, ABG	X	→	→	→	→	→	→	→	→	→	X	X	X		X
Nutrition (SGA,NAF,UUN 24 hr)	X	→	→	→	→	→	→	→	→	→	X	X	X		X
SOFA, APACHE II	X	→	→	→	→	→	→	→	→	→	X	X	X		X
*US**	X	→	→	→	→	→	→	→	→	→	X	X	X	X	X
Muscle mass: BIVA	X	→	→	→	→	→	→	→	→	→	X	X	X	X	X
IC$	X	→	→	→	→	→	→	→	→	→	X	X	X		X
Optional: AA level, IgG, Lym	X	→	→	→	→	→	→	→	→	→	X	X	X		X
PCS score of SF-36													X	X	
28VFD=0															X

*US diaphragm and US femoral muscle
#Protein: Whey protein:1 scoop (5 g, 20 kcal) = protein 4 g, Peripheral vein:10% aminoven 500 ml (protein 50 g) or 10% amiparen 500 ml (protein 50 g), Central vein:15% aminoplasmal 500 ml (protein 75 g)
$ if available or no contraindications
CBC complete blood count, BUN blood urea nitrogen, Cr creatinine, LFT liver function test, ABG arterial blood gas, IC indirect calorimetry AA amino acid level, IgG Immunoglobulin level, Lym lymphocyte subpopulation, PCS Physical component summary

Table 2. Timeline of the study.

Month	**Activity plan**	**Outputs**
1-6	- Review literature and PICO initiating - Create the involved documents - Submit the research protocol to SIRB - Apply the grant - Start record the data as soon as possible	Approved the protocol by SIRB and start record the patients' data
7-12	Record the research data	Amount of population 25%
13-18	- Record the research data continuously - Prelim statistical analysis - Monitor complications	Amount of population at least 75%
19-24	- Completely record the patients' data - Data analysis - Complete the manuscript and prepare for submit the research	100% population and success to statistical analysis

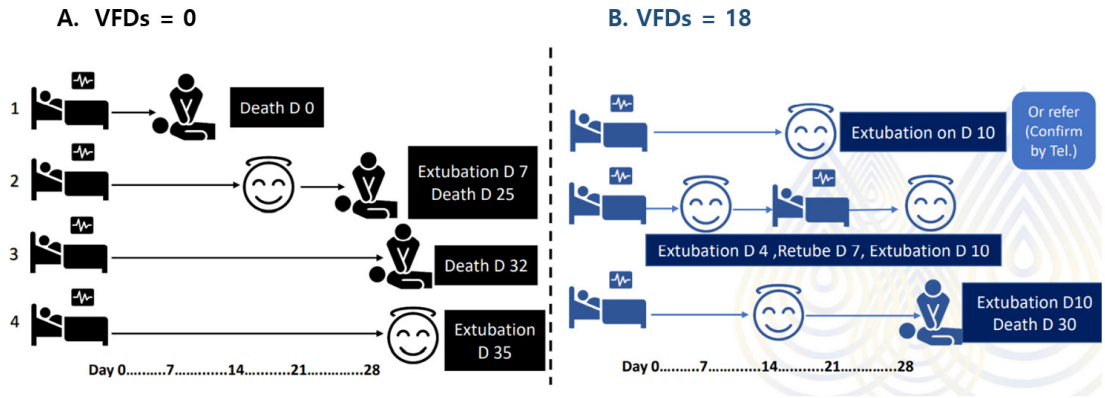

Figure 2. Definition of ventilator free days.

OUTCOME ANALYSIS PLAN

Statistical analyses

Descriptive statistics are obtained to report the baseline demographics and clinical variables of participants. Categorical variables are presented as the frequency (percentage), and continuous variables are presented as mean ± standard deviation or median (interquartile range). As regards, the baseline demographic data are compared using Chi-square or Fisher exact test as appropriate. In addition, comparison of the primary end point (VFDs at 28 day) is analyzed with independent T-test or Mann-Whitney U test as appropriate. Accordingly, the secondary outcomes in terms of mortality and infection rate are compared using Fisher exact test or Pearson test. Moreover, the PCS score of SF-36 is compared using T-test or Mann Whitney U test depending on the characteristic of the data. Finally, we analyze the change of muscle mass and SOFA score with linear mixed model as significant if p value is less than or equal 0.05.

Safety/feasibility analysis, adverse events, and interruption of trial

A safety monitoring was conducted by SIRB after 25% of total populations complete the study. The study will be continued only if both safety and feasibility are compatible. The study will be safety if no serious adverse events related to treatment in intervention group while the allocated treatment is on process.

Serious adverse events are defined as the event which is immediately life threatening or fatal, severely incapacitating, permanently disabling or need to prolong hospitalization or intensive care unit. The serious adverse events have to consider which are related to the treatment if the attending physician concern, the intervention need to be stop. The serious events in this study include developing acute kidney injury in term of creatinine rising ≥ 0.3 mg/dl within 48 hours or increasing ≥ 1.5 times baseline and blood urine nitrogen rising > 20 mg/dl/day.

Populations monitored total calorie intake and total protein diet per day, including gastrointestinal complications such as feeding intolerance, diarrhea and so on. Moreover, we followed SOFA score, nutritional status (NAF, SGA), muscle mass by BIVA and blood chemistry (albumin, prealbumin, CRP) every week of study duration. We collect the urine urea nitrogen 24 hours and ultrasound diaphragm (TPIA, excursion and thickness fraction) for clinicals alteration. The patients' data have already been confidential documents. We will apply the protocol to critical trials.gov, consequently, we will complete the manuscript within 30 days after finishing the enrollment.

DISCUSSION

There are insufficient data to establish the optimal amount of protein in mechanically ventilated patients; therefore, recent clinical guidelines suggest varying protein doses with low quality of evidence [1,16]. Although protein doses should be individualized based on patient's conditions, adding more protein is convincing and may improve patient-centered outcome. Our prospective randomized study will provide more robust evidence regarding whether high protein supply is beneficial.

As mentioned previously, existing RCTs showed mixed results. EAT-ICU study [11] compared early goal-directed nutrition versus standard of care in which the patients received 1.47 and 0.5 g/kg/d of protein respectively. However, there were no differences in clinical outcomes including long-term quality of life. Another study from Japan [13] comparing 1.5 vs. 0.8 g/kg/day of protein delivery revealed that the loss of femoral muscle volume was lower in the former group but only with active early rehabilitation. In addition, an RCT by Gordon S. Doig et al. [14] compared between 100 g of IV amino acids provision (about 1.75 g/kg/d) and standard care in 474 patients. They demonstrated that the duration of kidney dysfunction was not different.

Our study proposal aims to provide 2 different protein doses with comparable energy intake between groups to ensure the sole effect of protein. Protein supplementation can be used to achieve protein target in case of inadequate amount of protein in the EN or PN formula. VFDs at 28 days are used as the primary outcome since they are common composite endpoint combining survival and ventilator duration in mechanically ventilated patients [19]. As a potential favorable effect of protein supplementation for enhancing recovery, we hypothesize that high protein intake may contributes to longer VFDs.

CONCLUSION

The paucity of solid evidence leads to uncertainty regarding optimal protein intake in critically ill population. The present study will determine the clinical effect of high protein delivery and add more insight for the appropriate nutrition prescription in the ICUs.

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