

Effect of postoperative enteral protein supplementation on nitrogen balance in critically ill children

Irene Yuniar, MD, PhD, Kadek Apik Lestari, MD, Antonius Hocky Pudjiadi, MD, PhD, Fatima Safira Alatas, MD, PhD, Yoga Devaera, MD

Department of Child Health, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia

Background: Critically ill children are at risk of postoperative malnutrition. Thus, optimal nutritional therapy is essential for preventing morbidity development and reducing mortality rates among this population. An adequate protein intake increases anabolism. However, data on the effect of enteral protein supplementation on nitrogen balance (NB) and intestinal fatty acid-binding protein (I-FABP) levels in postoperative critically ill children remain limited.

Purpose: This study aimed to analyze whether an increased protein intake via enteral nutrition improves NB and reduces serum I-FABP levels among postoperative critically ill children.

Methods: This double-blind randomized controlled trial examined critically ill children aged 1–5 years who received early postoperative enteral nutrition. A total of 76 subjects were randomized into a standard-protein group (3.0 g/100 mL) or a high-protein group (4.35 g/100 mL). NB was assessed on days 1 and 3, while I-FABP levels were measured before and after 72 h of enteral feeding.

Results: The high-protein group showed a significantly greater increase in average NB (283.4 [standard deviation, 82.5] mg/kg/day) compared to the standard-protein group (114.7 [standard deviation, 53] mg/kg/day) ($P < 0.0001$). However, no significant decrease in I-FABP levels was noted in either group despite the above- and below-average NB improvements.

Conclusion: High-protein enteral supplementation improves NB in postoperative critically ill children without causing adverse side effects.

Key words: Protein, Supplement, Enteral nutrition, Critical illness, Pediatric intensive care unit

Key message

Question: Does high-protein enteral nutrition better increase the average nitrogen balance (NB) and decrease the intestinal fatty acid-binding protein (I-FABP) level of critically ill postoperative children than standard-protein enteral nutrition?

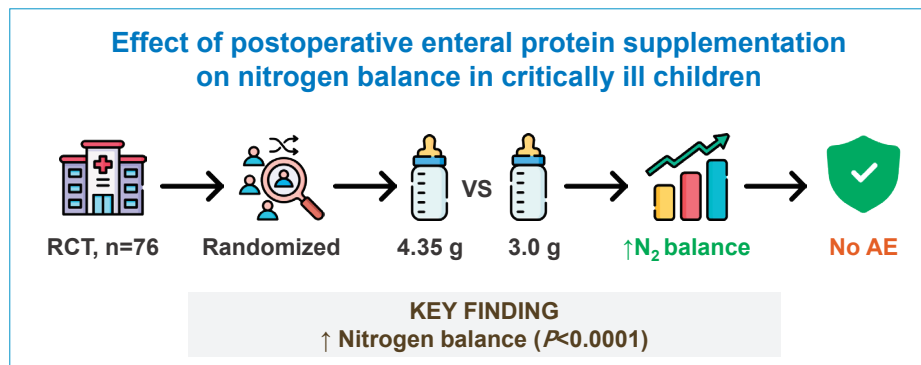
Finding: The study demonstrated a significant increase in average NB but no significant decrease in I-FABP levels in the high- versus low-protein group.

Meaning: These findings suggest that high-protein enteral nutrition can improve NB in critically ill postoperative children, thereby supporting their recovery.

Introduction

Surgery triggers a systemic acute phase response, activating the production of catabolic hormones such as cortisol and catecholamines.^{1,2)} This postsurgical catabolic state increases the risk of malnutrition.^{3,4)} Studies report that up to 48.9% of pediatric patients experience malnutrition upon admission to the pediatric intensive care unit (PICU), with two-thirds showing a decline in nutritional status during treatment.^{5,6)} In 2021, the incidence of malnutrition among postsurgical pediatric patients in the PICU at Cipto Mangunkusumo Hospital (RSCM), Jakarta, Indonesia, was alarmingly high: 51.92% experienced malnutrition, and 7.69% suffered from severe malnutrition.³⁾

Several studies in PICUs have reported inadequate protein and energy intake, ranging from 37% to 87% of patients' daily target requirements.^{7–10)} A 2014 study at RSCM found that 66.7% of patients had insufficient caloric intake, 86.67% were underfed in protein, and 60% did not meet their fat intake requirements.⁵⁾ Protein intake of $\geq 60\%$ of the prescribed amount is associated with lower 60-day mortality.⁹⁾ According to the latest recommendations



Graphical abstract. RCT, randomized controlled trial; AE, adverse side effects.

from the American Society for Parenteral and Enteral Nutrition (ASPEN), a minimum protein intake of 1.5 g/kg/day is required to achieve a positive nitrogen balance (NB) in critically ill children.¹¹⁻¹³ In postsurgical children, this minimum can increase to 120%–125% if wound healing is suboptimal.^{7,14} High-protein intake not only enhances NB but also increases serum protein levels, including amino acids, retinol-binding protein, and prealbumin.^{7,12-17} While high-dose protein intake is generally well-tolerated, in children older than 1 month, protein intake exceeding 3 g/kg/day may lead to elevated blood urea nitrogen levels.¹⁸

Protein supplementation can serve as an alternative to increase protein intake.¹⁹ According to the Society of Critical Care Medicine-ASPEN collaborative guidelines, parenteral nutrition is not recommended within 48 hours of PICU admission, making enteral nutrition a viable option for critically ill children. Early enteral nutrition is safe for patients after gastrointestinal resection surgery and leads to a 45% reduction in postoperative complications.²⁰ Enteral protein supplementation affects not only protein metabolism but also has the potential to improve intestinal permeability dysregulation, a common issue in post-surgical conditions due to tissue hypoperfusion and ischemia.²¹⁻²⁴ Dysregulated gastrointestinal permeability causes enterocyte damage, which is marked by an increase in the biomarker intestinal fatty acid-binding protein (I-FABP) in blood or urine.²⁵⁻³² Studies show that I-FABP levels can significantly increase after surgery, reflecting physiological stress. This increase suggests that I-FABP is not only a biomarker of intestinal injury but also a useful marker for monitoring postsurgical tissue perfusion. Improving NB is expected to reduce I-FABP levels, indicating repair of enterocyte damage.^{21,32-36} The aim of this study was to investigate the effect of enteral protein supplementation on NB and I-FABP levels in critically ill children after surgery.

Methods

1. Study design and setting

This study was a double-blind, randomized, controlled clinical trial aimed at assessing the effectiveness of high-protein enteral nutrition compared to standard-protein nutrition in critically ill pediatric patients after surgery. It was conducted in the PICU and cardiac intensive care unit (CICU) of RSCM, a referral hospital in Indonesia. Patient recruitment and randomization occurred between July 11 and October 29, 2024.

2. Ethical considerations

This trial was designed and conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocol was reviewed and approved by the Ethics Committee of the Faculty of Medicine, University of Indonesia - Cipto Mangunkusumo Hospital (code: KET-805/UN2.F1/ETIK/PPM.00.02/2024) and registered with ClinicalTrials.gov (code: NCT06411873). Informed consent was voluntarily obtained from the parents of all children enrolled in the trial prior to participation.

3. Study populations

The study subjects were pediatric patients aged 1 to 5 years who were critically ill postsurgery. Eligible patients were hemodynamically stable postsurgery. They had received enteral nutrition within 48 hours postsurgery and could be observed and examined within 72 hours after enteral nutrition administration. Exclusion criteria included patients with absolute contraindications to enteral nutrition (paralytic/mechanical ileus, gastrointestinal obstruction, gastrointestinal perforation) or relative contraindications (gastrointestinal dysmotility, necrotizing enterocolitis, toxic megacolon, extensive peritonitis, gastrointestinal bleeding, gastrointestinal fistula), a history of cow's milk allergy or use of special formula milk, ongoing breast milk feeding, high risk of refeeding syndrome according to the ASPEN consensus, acute or chronic

kidney disorders, liver disorders, diabetes mellitus, inborn metabolic disorders, total parenteral nutrition, continuous renal replacement therapy, or extracorporeal membrane oxygenation. Patients for whom NB could not be measured were also excluded. Dropout criteria included complications or intolerance to enteral nutrition, death during the study, resurgery during the study, transition to solid food nutrition, failure to conduct urine or blood tests, and withdrawal by the family.

The sample size ($n=38/\text{group}$) was calculated to detect a 150 mg/kg/day difference in NB (SD [standard deviation]=80, $\alpha=0.05$, power=80%), based on pilot data. Post hoc sensitivity analysis confirmed this provided adequate power (82%) even after stratifying by surgery type (cardiac vs. noncardiac). Subjects were randomly allocated to 2 diet groups using block randomization in blocks of 4 by the methodology team. The randomization table was provided to the dietitian by the methodology team, and the researchers were unaware of its contents. Allocation masking was implemented through sealed, sequentially numbered envelopes. Both researchers, patients, patient families, nurses, and treating doctors were blinded to the type of enteral nutrition the subjects received.

4. Intervention

Enteral nutrition was administered for 72 hours. The standard-protein group received a commercially available enteral formula (Pediacomplete, Abbott, Indonesia) providing 3.0-g protein, 13.3-g carbohydrate, 4.0-g lipids, and 100 kcal per 100 mL. The high-protein group received the same base formula supplemented with an additional 1.5-g protein/100 mL (PURO ISOPRO WPI Whey Isolate PLAIN,

Puro Pure Nutrition, Indonesia; BPOM: MD 862312050010), resulting in 4.35-g protein, 13.3-g carbohydrate, 4.0-g lipids, and 105.5 kcal per 100 mL. Both formulas were isoosmolar (standard, 310 mOsm/L; high-protein, 333.5 mOsm/L) and adhered to safety limits for pediatric enteral nutrition. The high-protein formula provided 4.35 g/100 mL (vs. 3.0 g/100 mL standard), delivering 2.3 g/kg/day—a 44% increase over standard intake and exceeding ASPEN minimums to target postsurgical anabolism. Formula compositions met ASPEN guidelines for pediatric enteral nutrition.¹⁸⁾ The high-protein formula's renal solute load (RSL) (27.7 mOsm/100 kcal) was within safe thresholds for infants (<39 mOsm/100 kcal). The bottles were prepared and delivered by a dietitian to each room.

Maintenance fluid and calorie requirements were calculated using the Schofield weight height formula with the addition of stress factors. Enteral nutrition was initiated at 2.5 mL/kg per feeding every 3 hours, delivered via an infusion pump over 1 hour. After 4 feedings, symptoms and signs of complications or intolerance were evaluated. If no complications or intolerance occurred, the enteral nutrition dose was increased by 5 mL/kg per feeding every 3 hours. After an additional 4 feedings, the dose was increased by 7.5 mL/kg per feeding every 3 hours, and after 4 more feedings, the dose was increased by 10 mL/kg per feeding every 3 hours, continuing until the target calorie requirement was reached.

In both groups, if complications or intolerance occurred, enteral nutrition was paused for 1 hour and then reevaluated. If no issues were identified, the nutrition dose was increased to the target level. If problems persisted, enteral nutrition was paused for 3 hours, and parenteral

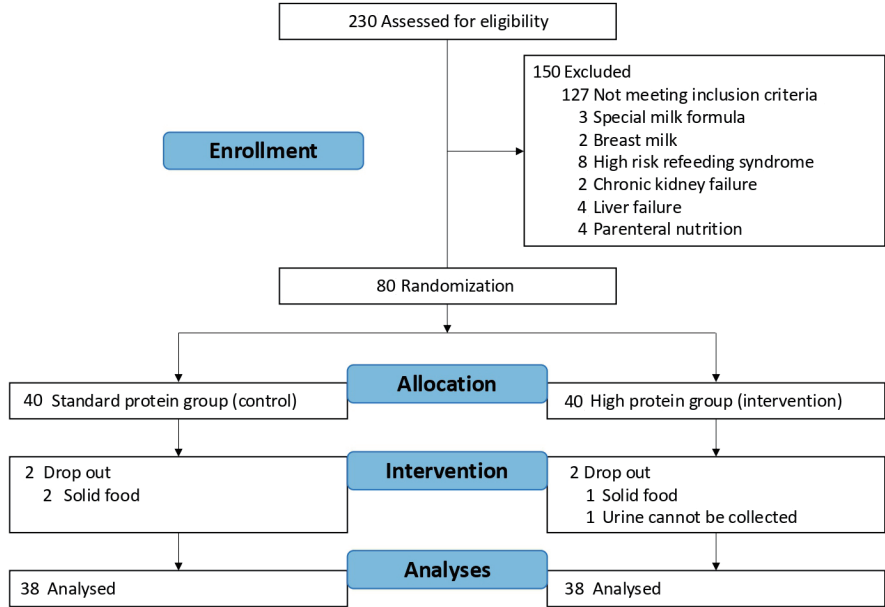


Fig. 1. CONSORT (Consolidated Standards of Reporting Clinical Trials) flow diagram.

nutrition was started. If complications continued, enteral nutrition was discontinued, and parenteral nutrition was considered, leading to the subject's dropout from the study. Medications for managing complications or side effects were administered according to PICU/CICU protocols, based on the evaluation of the on-duty doctor and the responsible physician's decision. In cases of severe metabolic acidosis or acute kidney failure, the pseudonym code from the subject's randomization table was unlocked.

5. Data collection

Before administering enteral nutrition, data were collected and recorded in the research form, including patient identity, demographics, clinical and supporting data, anthropometric measurements, and medications enteral nutrition, in terms of volume, calories, and protein, was recorded daily for 72 hours. In both groups, NB was assessed after the first and third 24-hour periods of enteral nutrition. NB was determined by subtracting nitrogen losses from nitrogen intake, which includes urinary, fecal, and miscellaneous losses (such as dermal, sweat, and integumentary losses). The calculation is represented by the following formula¹⁹:

$$\text{NB (mg/kg)} = \text{nitrogen intake (mg/kg)} - (\text{total urine nitrogen [mg/kg]} + 75 \text{ mg/kg})$$

Here, 75 mg/kg accounts for fecal and miscellaneous nitrogen losses. Total urinary nitrogen excretion was calculated by multiplying the urinary urea nitrogen concentration (mg/kg) by 1.25, to account for additional nitrogen losses in the form of ammonia, creatinine, uric acid, and amino acids. A conversion factor of 6.25 was used to estimate nitrogen intake from protein intake, reflecting the average amount of nitrogen found in 1 gram of protein. The urinary urea nitrogen examination using a 24-hour urine sample collection was performed at the PRODIA laboratory (Indonesia), along with blood I-FABP level measurements (Quantikin ELISA Human FABP2/I-FABP; R&D Systems, Inc., USA). Serum I-FABP, electrolytes (Na⁺, K⁺, Cl⁻), urea, creatinine, and albumin were measured at baseline and 72 hours. Artery blood gas (pH, HCO₃⁻) was analyzed at the same timepoints. Urine urea nitrogen (UUN) was collected over 24 hours for NB calculations. Enteral complications were recorded to evaluate the safety and efficacy of enteral protein supplementation.

6. Statistical analysis

The primary outcome was the NB delta in mg/kg/day (1st 24 hours NB – 3rd 24 hours NB) and the change from baseline to the final assessment of blood I-FABP levels. All data were analyzed using IBM SPSS Statistics ver. 26.0 (IBM Co., USA). Qualitative variables were analyzed using

the chi-square test. The normality of variable distribution was assessed with the Shapiro-Wilk test. Quantitative variables with normal distribution were evaluated using the Independent samples *t* test. The nonparametric Mann-

Table 1. Characteristics of the research subjects

Characteristic	Standard-protein group (n=38)	High-protein group (n=38)
Sex		
Male	17 (44.7)	20 (52.6)
Female	21 (55.3)	18 (47.4)
Age (yr)	3.0 (1.8–4.0)	2.0 (1.0–3.0)
Weight (kg)	11.3 (9.6–14.7)	10 (8.8–12.2)
Length/height (cm)	93.0 (77.0–105.3)	82.0 (74.5–95.0)
Weight/age (z score)	-1.29±1.35	-1.33±1.50
Height/age (z score)	-1.21±1.29	-1.6±1.68
Weight/height (z score)	-1.07±1.37	-0.71±1.41
Operation plan		
Elective	35 (92.1)	37 (97.4)
Cito	3 (7.9)	1 (2.6)
ASA PS classification grade		
II	16 (42.1)	11 (28.9)
III	22 (57.9)	27 (71.1)
Operation type		
Abdomen	13 (34.2)	13 (34.2)
Nonabdomen	25 (65.7)	25 (65.8)
Operation duration (min)	253 (161–306)	245 (178–363)
Analgesia sedation drugs		
Yes	24 (63.2)	29 (76.3)
No	13 (36.8)	9 (23.7)
Vasoactive drugs		
Yes	15 (39.5)	12 (31.6)
No	23 (60.5)	25 (68.4)
Muscle relaxant drugs		
Yes	0 (0)	1 (2.6)
No	38 (100)	37 (97.4)
Corticosteroid drugs		
Yes	5 (13.2)	6 (15.8)
No	33 (86.8)	32 (84.2)
Ventilator		
Yes	21 (55.3) ^{a)}	31 (81.6)
No	17 (44.7)	7 (1.4)
Ventilator duration (day)	1 (0–3)	1 (1–2.25)
PELOD-2 score		
≤11	38 (100)	38 (100)
>11	0 (0)	0 (0)
VIS score	4 (6.1)	4 (6.1)
Fasting time (hr)	30 (18–37)	30 (21–32)
Length of stay PICU/CICU (day)	5 (3–6) ^{b)}	3 (2–5)
Length of stay in hospital (day)	10 (7–17)	9 (7–14)

Values are presented as number (%), median (interquartile range), or mean±standard deviation.

ASA PS, American Society of Anesthesiologists physical status; CICU, cardiac intensive care unit; PELOD-2, Paediatric Logistic Organ Dysfunction-2; PICU, pediatric intensive care unit; VIS, vasoactive-inotropic score.

P<0.05 versus the high-protein group (chi-square test^{a)}, Mann-Whitney *U* test^{b)}). The mean nutritional status (underweight defined as weight/age *z* score < -2) did not differ between groups (*P*=0.79).

Whitney *U* test was used to compare median values. Significance was set at a *P* value of <0.05.

Results

A total of 76 subjects completed the study. A CONSORT (Consolidated Standards of Reporting Clinical Trials) flow diagram of this trial is presented in Fig. 1. Thirty-eight subjects were included in the control group (receiving standard-protein enteral nutrition of 3-g protein/100 mL), and 38 subjects were included in the treatment group (receiving high-protein enteral nutrition of 4.35-g protein/100 mL). The characteristics of the subjects are presented in Table 1. There were no significant differences in subject characteristics between the 2 groups, except for the use of ventilators and PICU/CICU length of stay. The proportion of underweight subjects was comparable between the standard-protein (31.7%) and high-protein (29.0%) groups (*P*=0.79), confirming balanced baseline nutritional status.

The characteristics of enteral nutrition provided to both groups are presented in Table 2. In both groups, 32 subjects (42.1%) achieved the target calorie requirements based on the resting energy expenditure calculation at 48 hours

after enteral nutrition administration. The high-protein group received significantly greater protein intake than the standard-protein group, with a mean difference of 0.7 g/kg/day (95% confidence interval, 0.6–0.8).

In the standard-protein group, only 5 subjects (13.2%) had a positive NB after the first 24 hours of enteral nutrition, and 34.2% remained in a negative NB until the end of monitoring (the third 24 hours). In the high-protein group, 14 subjects (36.8%) had a positive NB after the first 24 hours of enteral nutrition. By the end of monitoring, there was a significant increase, with 37 subjects (97.4%) achieving a positive NB, and only 1 subject (2.6%) remaining in a negative NB in the high-protein group. The NB delta was significantly higher in the high-protein group compared to the standard-protein group, with a mean difference of 168.7 mg/kg/day (Table 3). The average delta NB was used as the cutoff point for dividing the NB groups into below-average or above-average. In post hoc analysis, the high-protein group showed consistent NB improvements across surgical subtypes: cardiac surgery: ΔNB = 270.2 mg/kg/day (vs. 110.5 in standard-protein; *P*=0.003); abdominal surgery: ΔNB = 289.1 mg/kg/day (vs. 118.3; *P*<0.001); other surgeries: ΔNB = 265.4 mg/kg/day (vs. 112.0; *P*=0.002).

There were 21 subjects (27.6%) who had very high preenteral I-FABP levels (>5,000 pg/mL), consisting of 11 subjects after cardiac surgery, with the rest having undergone abdominal surgery, ventriculoperitoneal shunt, or suffered crush injuries. Postcardiac surgery subjects had a median preenteral I-FABP level of 3,458 pg/mL (interquartile range [IQR], 2,278–6,189 pg/mL), which was significantly higher than that of other postsurgery subjects. Subjects with underweight nutritional status had a median preenteral I-FABP level of 3,626 pg/mL (IQR, 1,891–5,733 pg/mL), which was significantly higher than

Table 2. Enteral volume, energy, and protein intake over 72 hours by study group

Variable	Standard-protein group (n=38)	High-protein group (n=38)	<i>P</i> value
Enteral volume (mL/kg/day)	52.8±4.0	51.5±3.8	0.14
Enteral energy (kcal/kg/day)	52.9±3.9	54.6±4.3	0.07
Enteral protein (g/kg/day)	1.6±0.1	2.3±0.2	<0.001 ^{a)}

Values are presented as mean±standard deviation. Boldface indicates a statistically significant difference with *P*<0.05. ^{a)}Independent samples *t* test.

Table 3. Nitrogen balance by study group

Variable	Standard-protein group (n=38)	High-protein group (n=38)	<i>P</i> value
Nitrogen balance (mg/kg/day)			0.064
1st 24 hr	-87.52 (-160.75 to -30.52)	-33.55 (-126.23–21.35)	
3rd 24 hr	30.05 (-40.48 to 82.97)	244.26 (179.11–302.32)	<0.001 ^{a)}
Nitrogen balance delta (mg/kg/day)	114.7±53.0	283.4±82.5	<0.001 ^{b)}

Values are presented as median (interquartile range) or mean±standard deviation. Boldface indicates a statistically significant difference with *P*<0.05. ^{a)}Mann-Whitney *U* test. ^{b)}Independent samples *t* test.

Table 4. I-FABP level by study group

Variable	Standard-protein group (n=38)	High-protein group (n=38)	<i>P</i> value
I-FABP level (pg/mL)			
Before enteral	1,934 (1,502–3,657)	2,971 (1,503–5,347)	0.324
After enteral	814 (516–1,221)	758 (635–1,148)	0.629
Delta I-FABP (pg/mL)	-1,195 (-2,781 to -593)	-1,819 (-4,454 to -556)	0.391

Values are presented as median (interquartile range). I-FABP, intestinal fatty acid-binding protein.

Table 5. I-FABP level by nitrogen balance by study group

Variable	Standard-protein group			High-protein group		
	Nitrogen balance increases under average (n=19)	Nitrogen balance increase over average (n=19)	P value	Nitrogen balance increase under average (n=22)	Nitrogen balance increase over average (n=16)	P value
Level of I-FABP (pg/mL)						
Before enteral	1,708 (1,209–4,253)	2,366 (1,760–3,459)	0.223	1,929 (1,335–5,127)	3,746 (1,775–5,823)	0.153
After enteral	848 (567–1,213)	609 (459–1,246)	0.686	763 (650–1,140)	717 (597–1,385)	0.849
Delta I-FABP (pg/mL)	-927 (-3,040 to -506)	-1,370 (-2,781 to -1,370)	0.311	-1,351 (-3,884 to -304)	-2,674 (-4,806 to -824)	0.122

Values are presented as median (interquartile range).

I-FABP, intestinal fatty acid-binding protein.

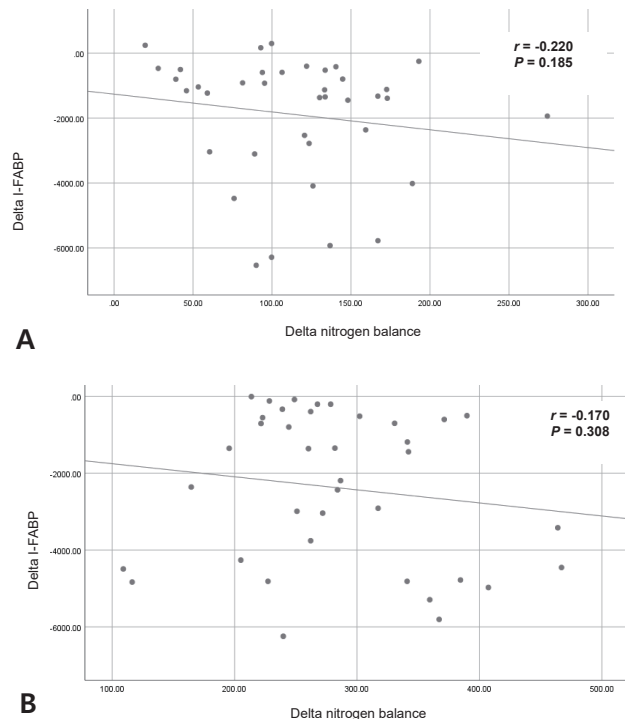


Fig. 2. Correlation between delta nitrogen balance and delta I-FABP level. (A) Standard-protein group. (B) High-protein group. I-FABP, intestinal fatty acid-binding protein.

subjects with normal nutritional status or those who were overweight. In the study, the median I-FABP levels before and after enteral administration did not differ between the 2 groups (Table 4). The delta I-FABP levels showed a greater decrease in the high-protein group compared to the standard-protein group, though the difference was not significant.

There was no significant difference in the decrease of I-FABP levels between the group of subjects who experienced an increase in NB above the average and the group who experienced an increase below the average (Table 5). The correlation between delta NB and delta I-FABP levels was low and insignificant in both groups (Fig. 2). This study evaluated the occurrence of side effects in critically ill children after surgery who received standard-protein and high-protein enteral nutrition. The high-protein group showed 2 cases of vomiting, while the

Table 6. Side effects of standard- versus high-protein enteral nutrition

Variable	Standard-protein group (n=38)	High-protein group (n=38)
Side effects		
Increased gastric residual volume	0 (0)	0 (0)
Vomiting	1 (2.6)	2 (5.3)
Diarrhea	0 (0)	0 (0)
Abdominal distension	0 (0)	1 (2.6)
Melena	0 (0)	0 (0)
Hematemesis	0 (0)	0 (0)
Rash	0 (0)	0 (0)
Metabolic acidosis	0 (0)	0 (0)
Hyperuricemia	0 (0)	0 (0)
Refeeding syndrome sign	0 (0)	0 (0)

Values are presented as number (%).

Table 7. Serum biochemical markers after 72-hour enteral nutrition period

Marker	Standard-protein group (n=38)	High-protein group (n=38)	P value
Na ⁺ (mEq/L)	138 (136–140)	137 (135–139)	0.32
K ⁺ (mEq/L)	4.1 (3.8–4.3)	4.2 (3.9–4.4)	0.45
Cl ⁻ (mEq/L)	102 (100–104)	103 (101–105)	0.28
Urea (mg/dL)	12.9 (12.3–14.0)	15.9 (15.0–17.0)	0.02
Creatinine (mg/dL)	0.4 (0.3–0.5)	0.5 (0.4–0.6)	0.15
Albumin (g/dL)	3.2 (2.9–3.5)	3.3 (3.0–3.6)	0.45
pH	7.35 (7.32–7.38)	7.34 (7.30–7.37)	0.60
HCO ₃ ⁻ (mmol/L)	22 (20–24)	21 (19–23)	0.25

Values are presented as median (interquartile range).

Boldface indicates a statistically significant difference with $P < 0.05$.

standard-protein group had only one case. This difference was not statistically significant. There was one case of abdominal distension in the high-protein group, while none was observed in the standard-protein group. No cases of increased gastric residual volume, diarrhea, melena, hematemesis, rash, metabolic acidosis, hyperuricemia, or signs of refeeding syndrome were recorded in either group. No subjects died during the study period (Table 6). The median urea level after enteral nutrition in the standard-protein group was 12.85 (IQR, 12.3–14) mg/dL, while in the high-protein group, it was 15.9 (IQR, 15–17) mg/dL (Table 7).

Discussion

The high-protein group showed a higher ventilator requirement than the standard-protein group. The higher ventilator requirement in the high-protein group indicates that patients in this group experienced more severe clinical conditions or had further complications requiring respiratory support after surgery. The use of mechanical ventilators causes myotrauma, which induces proteolysis, inflammation, and mitochondrial dysfunction, which are positively correlated with the occurrence of negative NB.^{4,8,9)} Proteolysis due to oxidative stress occurs after ventilator use >72 hours. Prolonged ventilator use (>7 days) is significantly associated with negative NB.³³⁾ In this study, the need for higher ventilator use can be a risk factor for negative NB, but there was no significant difference in the duration of ventilator use in the 2 groups. So, the risk of a more negative NB in the high-protein group did not occur.

In this study, it was found that the length of stay in PICU/CICU in the high-protein group was shorter. A study of enteral nutrition that divided 3 groups of subjects (standard-protein, high protein, and very high protein) obtained different results; the length of stay in PICU was not significantly different.¹⁹⁾ However, in this study, no significant difference was found in the length of stay in the hospital between the 2 groups. This suggests that high-protein enteral nutrition therapy in critically ill children after surgery can reduce the length of stay in the intensive care unit and contribute to faster recovery after surgery.

In this study, there was no significant difference in the mean volume and calories of enteral nutrition given to both groups. A study in children aged 1 month to 16 years obtained similar results. After 5 days of enteral nutrition, there was no significant difference in the mean calories in the standard-protein group (65.9 kcal/kg/day) and the high-protein group (71.9 kcal/kg/day).¹²⁾ Because of the provision of enteral volume and calorie intake did not differ significantly in the 2 groups, it did not become a confounding factor in the effect of high-protein intake on changes in NB.

Daily protein intake in the high-protein group was significantly greater than that in the standard-protein group. Studies using 3 different amounts of enteral nutrition protein also obtained similar results, the protein intake of the standard-protein group (1.7 ± 0.6 g/kg/day), the high-protein group (2.2 ± 0.8 g/kg/day), and the very high-protein group (3.4 ± 1.2 g/kg/day).¹⁹⁾ These results are consistent with several other studies of enteral protein supplementation.^{12,17,19,21)} While 'high protein' lacks a universal threshold, our intervention (2.3 g/kg/day) aligns with studies demonstrating improved outcomes in critically ill child-

ren²¹⁾ and reflects real-world feasibility in fluid-restricted patients.

In this study, overall, 75% of subjects experienced negative NB after the first 24 hours of enteral nutrition. A study of critically ill children aged <12 months who were treated in the PICU due to respiratory failure found that 72.4% of subjects experienced negative NB at the start of enteral nutrition.¹⁹⁾ Slightly different results in a study of children aged <12 months after cardiac surgery found negative NB in all study subjects at the start of enteral nutrition. This difference in results can be explained by several factors that have been identified to increase the risk of negative NB, such as younger age of the child, inadequate energy and protein intake, parenteral nutrition route, severity of illness, length of PICU stay, and length of immobilization.^{13,22-26)}

In the high-protein group, there was a significant increase in subjects who achieved positive NB, and only 1 subject (2.6%) was still negative at the end of monitoring, while in the standard-protein enteral nutrition group, there were still 34.2% of subjects with negative NB. The outlier subject's persistent negative NB likely reflects extreme catabolism postcardiac surgery, exacerbated by preoperative malnutrition and prolonged mechanical ventilation. Despite high-protein intake (2.4 g/kg/day), systemic inflammation and immobilization may have prolonged protein breakdown, as observed in similar cases.³⁷⁾ Transient abdominal distension necessitated a 20% reduction in enteral volume on day 2, delaying calorie/protein delivery. This aligns with studies showing that feeding interruptions worsen NB in critically ill children.³³⁾ The subject's elevated I-FABP (5,200 pg/mL) suggested significant gut injury, which may have impaired nutrient absorption. Notably, their NB improved from -210 to -45 mg/kg/day, indicating a partial response to protein supplementation despite persistent negativity. This case underscores that high-protein enteral nutrition may not fully overcome nitrogen losses in severely catabolic patients, particularly those with: preoperative malnutrition (low lean mass reserves), major cardiac surgery (prolonged inflammation), or feeding intolerance (interrupted delivery). Individualized monitoring (e.g., sequential NB assessments) is critical for such high-risk subgroups.

One of the targets of nutritional therapy in critically ill children after surgery is to achieve a positive NB as soon as possible so that the child does not lose total lean tissue mass. A positive NB indicates that protein intake or synthesis is higher than excretion, which is expected to accelerate the anabolic phase, which is an ideal condition for healing and growth. In this study, a significant increase in the average NB was found in critically ill children after surgery who received high-protein enteral nutrition com-

pared to those who received standard protein. These results indicate that higher protein supplementation has a significant impact on increasing NB. These results are in accordance with a study in pediatric patients with respiratory failure due to respiratory syncytial virus infection. The average increase in NB was greater in the high-protein enteral group, 297 ± 47 mg/kg/day, compared to those who received standard protein 123 ± 23 mg/kg/day.¹⁴⁾

Protein supplementation in enteral nutrition has been shown to significantly increase the content of essential amino acids (histidine, lysine, phenylalanine, methionine, and valine) and nonessential in the blood, compared to those who did not receive protein supplementation.^{14,31)} In addition to increasing protein synthesis, protein supplementation will help regulate catabolic and anabolic hormones. Adequate protein intake will stimulate the formation of anabolic hormones, namely insulin and insulin-like growth factor 1. Insulin will stimulate the absorption of amino acids into muscle cells and increase protein synthesis.³²⁾ The results of this study indicate that increasing enteral protein intake with protein supplementation will increase NB, which is expected to increase protein synthesis, increase anabolic hormone production, reduce catabolic hormone secretion, and improve insulin resistance.

Improving NB also has the potential to overcome disorders of the microbiome in the digestive tract. I-FABP is a biomarker used to detect intestinal tissue damage and tissue hypoperfusion. Plasma I-FABP levels can increase in postoperative conditions due to decreased tissue perfusion, which causes injury to enterocytes in the digestive tract. In this study, postoperative blood I-FABP levels before enteral nutrition administration increased quite high in both groups. In accordance with the results of observational studies in children aged <3 months after cardiac surgery, I-FABP levels increased significantly 6 hours after surgery and 24 hours after surgery compared to before surgery.³⁸⁻⁴¹⁾ Similar results were found in a study in children after gastroschisis surgery.^{38,39,42,43)}

The increase in I-FABP levels before enteral in this study may be due to the majority of subjects with post-abdominal surgery and postcardiac surgery with the use of cardiopulmonary bypass (CPB). The use of CPB can cause damage to enterocytes through several mechanisms related to ischemia-reperfusion and inflammatory reactions. In this study, the number of subjects with malnutrition had higher I-FABP levels before enteral. Higher I-FABP levels in malnutrition conditions can be caused by damage to intestinal villi epithelial cells due to malnutrition, tissue hypoperfusion, and oxidative stress, which contribute to increased cell permeability and tissue damage.

Studies on the relationship between I-FABP levels after enteral nutrition in critically ill children are still limited. This study found a decrease in I-FABP levels after 72 hours enteral nutrition in both groups. Early enteral nutrition in postoperative pediatric patients has an important role in maintaining enterocyte integrity and intestinal mucosal barrier function.³³⁻³⁶⁾ This study found a greater decrease in I-FABP levels in the group that experienced an increase in NB above the mean compared to the group of subjects who experienced an increase in NB below the mean, but it was not statistically significant. I-FABP is an indicator of cellular integrity and damage to the intestinal mucosa, so the absence of a significant difference in I-FABP levels may indicate that although NB has increased, improvements in the intestinal mucosa have not been seen enough at this measurement stage.^{38-40,42-44,45,46)}

Although adequate protein intake can support tissue repair, if there are other factors causing stress or damage to the intestine, I-FABP levels may remain high. In this case, despite adequate nutrition, effective nutrient absorption may be impaired, which may contribute to persistently high I-FABP levels due to ongoing intestinal damage.^{38,39,42,43)} Circulating I-FABP levels can be affected by the timing of measurement, either before or after the intervention. Several studies have shown that changes in I-FABP levels are not always immediately apparent after nutritional intervention.^{36,37,39-41,44-46)} A postcardiac surgery study found a decrease in I-FABP levels after 72 hours of surgery, while a study of gluten-free nutrition in children with celiac disease found a decrease in I-FABP only after 6 months of nutrition.³⁷⁾ Individual variability in response to stress and injury can also affect I-FABP levels.⁴²⁾ Therefore, although high-protein enteral nutrition shows great potential in improving NB and supporting microbiome health, its benefits have not been evaluated with I-FABP biomarkers. The clinical impact of this protein supplementation has also not been seen.

The lack of significant I-FABP reduction despite improved NB may reflect: (1) the 72-hour intervention period being too short for mucosal repair, as enterocyte turnover typically requires 5-7 days,⁴⁵⁾ (2) heterogeneity in surgical stress, particularly in cardiac cases where ischemia-reperfusion injury prolongs gut barrier dysfunction,³⁴⁾ and (3) the dominant role of systemic inflammation in early critical illness, which may delay biomarker normalization even with adequate protein intake.³⁵⁾ Future studies could extend monitoring to 7-14 days and explore adjunctive therapies (e.g., immunonutrition) to enhance gut repair. Although our results demonstrate significant improvements in NB within 72 hours, the lack of I-FABP reduction may reflect the need for longer intervention periods, as enterocyte repair often requires >1 week.³⁴⁾

Subsequent trials could stratify patients by surgical type and monitor biomarkers beyond the acute phase.

This study found that the high-protein group experienced 2 cases of vomiting and 1 case in the standard-protein group. There was one case of abdominal distension in the high-protein group. Abdominal distension occurred in the second 24 hours of enteral nutrition. After reducing the enteral volume and correcting electrolyte disorders in the subject, abdominal distension could be resolved, and enteral nutrition could be continued. In addition, this study found no reports of increased gastric residual volume, diarrhea, melena, hematemesis, rash, metabolic acidosis, hyperuricemia, or signs of refeeding syndrome in both groups, indicating that high-protein intake can be tolerated without causing significant gastrointestinal complications.^{16,17)}

Previous studies have shown that protein supplementation can increase the osmolality of formula, which may affect gastrointestinal tolerance.²¹⁾ The American Academy of Pediatrics recommends an osmolality of ≤ 460 mOsm for infant formula. In this study, the osmolality of the standard-protein enteral was 310 mOsm/L, while the high-protein enteral was 333.5 mOsm/L, not exceeding the recommended safe limit.

The provision of modular supplementation in children must take into account the child's kidney capacity because the limited capacity of the child's kidneys to concentrate and excrete nutrients, electrolytes, and unmetabolized metabolites can cause dehydration. The RSL that are safe for infants is <39 mOsm/100 kcal of formul. In this study, the high-protein group RSL was 27.7 mOsm/100 kcal. One thing that must be considered is excess protein intake which can cause excessive protein oxidation so that it has the potential to increase urea levels in the blood. Previous studies have shown that patients who receive high-protein enteral nutrition (5.1 g/100 mL) have higher urea levels and a greater incidence of hyperuricemia.²⁰⁾ Consistent with prior studies,¹⁷⁾ high-protein enteral nutrition increased serum urea without affecting electrolytes, creatinine, or acid-base balance. This supports the safety of 2.3 g/kg/day protein in critically ill children. While blood urea nitrogen levels were moderately higher in the high-protein group, all values remained within physiologic ranges, and no renal dysfunction was observed. This aligns with prior studies showing safe tolerance of 2.0–2.5 g/kg/day protein in critically ill children.¹⁷⁾ Notably, albumin and acid-base balance were unaffected, suggesting that short-term high-protein enteral nutrition does not disrupt broader metabolic homeostasis.

The advantage of this study is that it is the first study in Indonesia on the provision of enteral protein supplementation in critically ill children after surgery. The

protein supplementation given is well calculated so that it is safe to be given to the research subjects. Increasing the amount of protein intake does not significantly increase the amount of calorie intake and enteral volume, so it is suitable for children in critically ill conditions with fluid restrictions. In this study, all UUN results were the results of 24-hour urine collection, so the results obtained were more reliable. The disadvantage of this study is that the examination of NB and I-FABP was not carried out every day due to cost constraints. Our study was limited to 72 hours of monitoring, which may not capture later-phase changes in NB or I-FABP levels. Future studies should extend the observation period to 7–14 days to assess sustained effects, particularly in children with prolonged PICU stays. We did not measure long-term renal outcomes (e.g., 30-day epidermal growth factor receptor) or muscle protein synthesis markers (e.g., 3-methylhistidine), which could further clarify the metabolic impact. We did not measure urinary electrolytes or fractional excretion of urea, which could provide additional renal safety data. Future studies could incorporate these metrics. While our study included diverse surgical populations, subgroup analyses confirmed consistent effects of high-protein supplementation. However, larger trials stratifying by surgery type (e.g., cardiac vs. abdominal) may further validate these findings.

In conclusion, there was a significant increase in the average NB in the high-protein group compared to the standard-protein group. There was no significant difference in either the standard or high-protein groups between the decrease in I-FABP levels in the group of subjects who experienced an increase in NB above the average compared to the group of subjects who experienced an increase in NB below the average.

Footnotes

Conflicts of Interest: The authors declare no conflict of interest.

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ORCID:

Irene Yuniar  <https://orcid.org/0000-0002-0880-333X>

Kadek Apik Lestari  <https://orcid.org/0009-0000-1576-5581>

Antonius Hocky Pudjiadi  <https://orcid.org/0000-0002-5675-195X>

Fatima Safira Alatas  <https://orcid.org/0000-0003-1299-7154>

Yoga Devaera  <https://orcid.org/0000-0002-5427-9823>

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