

Initial caloric administration as a risk factor for mortality in critically-ill children

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Abstract

Background: The mortality rate of critically-ill children with multiple organ dysfunction syndrome (MODS) in Indonesia is approximately 51.85%. Various studies suggested malnutrition as a risk factor for mortality; therefore, nutrition therapy in the form of initial caloric administration became imperative.

Objective: To determine the relationship between initial caloric administration (initial route, initial time and the fulfilment of caloric requirement) and mortality of critically-ill children.

Design: Case-control study.

Setting: The Pediatric Intensive Care Unit (PICU) of Dr. Sardjito General Hospital Yogyakarta in 2015.

Patients and participants: Children aged 1 month to 18 years old hospitalized in the PICU for at least 4 days in 2015. Subjects were divided into case group (non-surviving patients) and control group (surviving patients).

Measurements and results: We used McNemar test and stepwise conditional logistic regression for data analysis. From 102 subjects (51 in each group), the proportion of malnourished children

in the case group was higher than in the control group (58.8% and 29.4%, respectively). Parenteral route and lack of caloric achievement within the 3rd to 6th day of hospitalization significantly increased the risk of mortality ($p < 0.05$) with ORs of 13 (95%CI 1.95 to 552.47), 3.8 (95%CI 1.37 to 13.02), 4.25 (95%CI 1.39 to 17.26), 4.00 (95%CI 1.08 to 22.09), and 10.0 (95%CI 1.42 to 433.98), respectively. Caloric initiation after the first 48 hours of hospitalization did not significantly affect the mortality rate ($p > 0.05$). Confounding variables that affected mortality include the severity of disease, use of ventilator, hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and malnutrition ($p < 0.05$). Multivariate analysis revealed that parenteral route and malnutrition significantly influenced mortality with ORs of 36.05 (95%CI 3.22 to 404.13) and 9.04 (95%CI 2.09 to 39.19), respectively.

Conclusion: There is a relationship between route of initial caloric administration and mortality of critically ill children, where parenteral nutrition significantly influenced mortality in critically ill children.

Key words: Critically ill, pediatric intensive care unit, mortality, nutrition therapy.

Introduction

Mortality is the most frequently assessed outcomes in PICU. The mortality rate of critically ill children with multiple organ dysfunction syndrome (MODS) in Indonesia is approximately 51.85%. (1,2) Risk factors for mortality in critically ill

children include lower socioeconomic status, severe diseases, MODS, comorbidities, different categories of primary diagnosis, long-term use of mechanical ventilator, high pediatric risk of mortality (PRISM) III score in the first 24 hours, poor nutritional status and previous health condition, use of total parenteral nutrition (TPN), use of vasoactive drugs, as well as healthcare-associated infections (HAIs) such as hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), surgical site infection (SSI), catheter-associated urinary tract infection (CAUTI), and central line-associated bloodstream infection (CLABSI). (2-8) Several studies have shown that malnutrition was associated with increased morbidity and mortality. (9-11) Percentages of severe malnutrition and undernourishment in Indonesia according to research by Riskedas (Indonesia's basic health research) in 2013 were 5.7% and 13.9%. The proportion of pa-

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tients admitted to PICU with malnutrition was approximately 19-32%, but malnutrition may also occur during hospitalization due to hypercatabolic condition that lowers body mass rapidly, weakens the function of vital organs, and impairs immune system, where all of these processes would absorb 30-50% of their energy. Thus, nutritional support in the form of initial caloric administration is a part of important treatment. Several aspects of the initial caloric administration that may affect mortality are the provision of parenteral route to initiate caloric administration, a delayed initiation of caloric administration, and the lack of caloric achievement. (12-14)

This study aims to investigate aspects of initial caloric administration (route of administration, initial time of administration, and the fulfilment of caloric requirements) in the management of critically-ill children treated in PICU and their effects on mortality.

Materials and methods

We conducted a case-control study using medical record data to assess the relationship between initial caloric administration (route, time, fulfilment) and the mortality of critically-ill children. The subjects were divided into case group (deceased patients from PICU) and control group (patients discharged from PICU alive). The subjects were chosen using total sampling technique based on inclusion and exclusion criteria and were matched for their age and sex. The inclusion criteria were critically-ill patients aged 1 month to 18 years old who were treated for at least 4 days (4x24 hours) in the PICU of Dr. Sardjito General Hospital, whose admission to the PICU was determined using the 1-3 priorities from the Society of Critical Care Medicine (SCCM) 2015. (15) The exclusion criterion was incomplete medical records.

The sample size for the paired case-control study with standard deviation of 5%, confidence interval of 95% (1.96) and power research of 90% was 50 in each group, at the minimum. The dependent variable was the patient's condition at the time of discharge from PICU (deceased or alive). The independent variables were the aspects of initial caloric administration including initial route of administration, initial time of administration, and the fulfilment of caloric requirement. The confounding variables were the primary diagnosis, severity of disease, the use of mechanical ventilator, nutritional status, and HAIs such as HAP, VAP, CAUTI, CLABSI and SSI. The study was conducted after being approved by the Ethical Committee of the Faculty of Medicine of Gadjah Mada University.

Data were collected using data collection form and were based on the patients' medical records. Data regarding aspects of the initial caloric administration was taken during the first 7 days of treatment in the PICU while data for confounding variables were taken during treatment in the PICU. We recalculated the patients' caloric requirement with Caldwell formula (for patients who with ventilators) or Schofield formula (for patients without ventilators), the daily fulfilment of caloric requirements, nutritional status, and PELOD scores in the first 24 hours of admission to the PICU to reduce the risk of information bias. For bivariate statistical analysis, we used the McNemar test, whereas the multivariate conditional logistic regression test were conducted using stepwise method where we incorporate variables with p value <0.25 from the bivariate test.

Results

There were a total of 102 subjects, divided into two groups, each consisted of 51 subjects. Basic characteristics of study subjects could be seen in **Table 1**.

Table 2 and **Table 3** present the results of the McNemar test on independent variables and confounding variables on the dependent variable. The use of parenteral route in initiating caloric administration and the lack of fulfilment of caloric requirement (<70% of caloric requirement) on the 3rd to 6th day of hospitalization significantly affected mortality, while delayed initiation (>48 hours after admission) did not affect mortality significantly.

Table 4 shows the results of the multivariate conditional logistic regression analysis using stepwise method, which shows that the parenteral route of initial caloric administration and malnutrition significantly increased the risk of mortality.

We conducted stratified analysis to discern the relationship between initial route administration for nutrition therapy and mortality rate by groups of nutritional status (good nutritional status and malnutrition) and the severity of the disease (severe and extremely severe groups). The initial route of administration affected mortality in patients with good nutritional status, but did not affect patients with malnutrition. It also affected mortality in patients with severe disease, but we could not analyze the group of patients with extremely severe disease since all patients in this group did not survive (**Table 5**).

Discussion

Malnutrition increased the risk of mortality signifi-

cantly in both bivariate and multivariate analyses. This finding was consistent with previous research by Prieto, et al and Bagri, et al stating the incidence of malnutrition in critically ill children was 25-70% and being malnourished may increase mortality in critically ill children. (9,16)

Parenteral route as an initial route of administration for caloric administration increased the risk of mortality compared to enteral route. (4,6) This was consistent with our results, as indicated by both bivariate and multivariate analyses. However, a results was obtained from meta-analysis by Elke, et al and Gramlich, et al where no significant difference was observed in terms of mortality between patients receiving enteral and parenteral nutrition. (17,18) This could be due to different sample size and the wide range of the confidence interval in our study, which required further research with a greater sample size. Complications of parenteral nutrition include underfeeding or overfeeding, metabolic complications (electrolyte disturbances, hypoglycemia, hyperglycemia, hypertriglyceridemia, and fatty liver), mechanical complications (pneumothorax, hemothorax, cardiac tamponade, air embolism, and equipment failure), as well as infection (sepsis and phlebitis). (19,20) Parenteral nutrition is associated with atrophy of the intestinal mucosa and bacterial translocation from the gut into the bloodstream, therefore increasing chances of infection and sepsis. Correlation between infection and parenteral nutrition may also be due to the complication related to the use of central venous catheters (CLABSI) or systemic infection related to hyperglycemic conditions. (21,22) The American Society for Parenteral and Enteral Nutrition (ASPEN) in 2016 recommends to keep parenteral route as an option in critically ill children, especially when enteral route cannot be provided or not sufficient for caloric administration. (23) It could be reduced by increasing the portion of enteral nutrition and discontinued gradually when enteral nutrition reaches 2/3 of total caloric needs. (19)

Table 5 shows that parenteral route of administration increased the risk of mortality in the group of patients with good nutritional status but not in the malnourished group. These results were due to the notion that malnutrition alone is a strong risk factor for mortality. This idea was supported by a study where a significant increase in incidence for complications were observed in malnourished patients, including infections, cardiopulmonary failure, and cardiac arrest, compared to patients with good nutritional status. (21) Parenteral route increased the risk of mortality in the group with severe disease but no conclusion could be drawn from extremely

severe group due to the fact that there were no surviving patients in this group. This was related to our limited samples size and supported by two previous studies, which suggested that the risk of mortality increases with a higher PELOD scores. (24,25)

Our findings suggested that the time of initial caloric administration had no significant effect on the risk of mortality. This result was in contrast to previous studies which suggest that early nutrition was associated with decreased mortality. (26,27) It was due to differences in characteristics of the study subjects. The two previous studies only involved subjects with mechanical ventilator, had bigger sample size, and used the initiation time of enteral nutrition as determination criteria for early and late feeding. Meanwhile our subjects involved all patients with and without mechanical ventilation, had smaller sample size, and used the initiation time of any route of administration (enteral or parenteral) to determine the criteria for early and late feeding.

The Ebb phase of metabolic stress in critically-ill children will last for 48-72 hours, followed by Flow phase (the hyperdynamic phase) that requires an adequate nutritional support to mobilize substance to produce energy. Based on this pathophysiology, it can be understood that the lack of caloric achievement from the third day of hospitalization will increase the risk of mortality. The longer time it takes for the caloric needs to be met, the higher the risk of mortality. Similar results were obtained from Mehta et al, where patients who fulfilled less than a third of their caloric requirements in the first 10 days of treatment had a higher risk of mortality and increased caloric achievement from 33% to 66% would reduce the risk of mortality significantly. (6)

Confounding factors that significantly affected mortality were the severity of the disease, the use of mechanical ventilator, HAP, VAP, and malnutrition. These were consistent with several previous studies. (2-5) As seen in **Table 3**, CAUTI, CLABSI, and SSI did not affect mortality due to the fact that the most frequent types of HAIs observed were HAP and VAP. This could also be due to limited variety and samples size, which could affect the primary diagnoses category. (8)

Several independent variables and confounding variables that were significant in the bivariate analysis ($p < 0.05$, **Tables 2** and **3**) became insignificant in the multivariate analysis ($p > 0.05$, **Table 4**) due to other more significant variables or strong correlation between independent variables and confounding variables. For example, the fulfilment

of caloric requirements would be influenced by the route of administration where enteral route of administration may certainly provide higher calories than parenteral route. The limitation of our study lay in the retrospective data collection that could lead to a biased information due to the fact that we did not directly follow the situation and just relied on information from the medical records. The method for calculating caloric requirements in the PICU of Dr. Sardjito General Hospital does not use indirect calorimetry yet as the gold standard and

therefore it may not fit the patients' actual requirement.

Conclusion

The only aspect of the initial caloric administration associated with risk of mortality in critically-ill children was initial route of administration. Parenteral route significantly influenced mortality in critically-ill children, while initial time of administration and the fulfilment of caloric requirement did not significantly affect mortality.

Table 1. Basic characteristic of study subjects

Characteristics	Case group (n=51)	Control group (n=51)
Age (years), mean (SD)	4.55 (5.46)	4.63 (5.46)
Sex, n (%)		
Male	28 (54.9)	28 (54.9)
Female	23 (45.1)	23 (45.1)
Nutritional status, n (%)		
Severe malnutrition	10 (1.6)	8 (15.7)
Undernourished	17 (33.3)	4 (7.8)
Good	21 (41.2)	36 (70.6)
Overweight	0 (0.0)	2 ((3.9)
Obese	3 (5.9)	1 (1.9)
Primary disease, n (%)		
Non-surgical	40 (78.4)	45 (88.2)
Digestive-surgical	8 (15.7)	2 (3.9)
Non digestive-surgical	3 (5.9)	4 (7.9)

Table 2. Bivariate analysis of independent variable and mortality

Variable	Case group	Control group	P	OR (CI95%)
Initial route, n (%)				
Parenteral	14 (27.5)	2 (3.9)	0.004*	13.0 (1.95-552.47)
Enteral	37 (72.5)	49 (96.1)		
Initial time, n (%)				
Late (> 48 hours since admission)	2 (3.9)	3 (5.9)	1.000	0.67 (0.06-5.82)
Early (≤ 48 hours since admission)	49 (96.1)	48 (94.1)		
Caloric achievement day 1, n (%)				
Less	44 (86.3)	44 (86.3)	1.000	1.00 (0.29-3.34)
Adequate	7 (13.7)	7 (13.7)		
Caloric achievement day 2, n (%)				
Less	34 (66.7)	26 (51.0)	0.169	1.89 (0.79-4.81)
Adequate	17 (33.3)	25 (49.0)		
Caloric achievement day 3, n (%)				
Less	28 (54.9)	14 (27.5)	0.007*	3.80 (1.37-7.13)
Adequate	23 (45.1)	37 (72.5)		
Caloric achievement day 4, n (%)				
Less	23 (45.1)	10 (19.6)	0.007*	4.25 (1.39-17.26)
Adequate	28 (54.9)	41 (80.4)		
Caloric achievement day 5, n (%)				
Less	22 (47.8)	12 (29.3)	0.035*	4.00 (1.08-22.09)
Adequate	24 (52.2)	29 (70.7)		
Caloric achievement day 6, n (%)				
Less	23 (52.3)	6 (18.8)	0.012*	10.0 (1.42-433.8)
Adequate	21 (47.7)	26 (81.3)		
Caloric achievement day 7, n (%)				
Less	15 (39.5)	5 (17.2)	0.063	- (0.92-∞)
Adequate	23 (60.5)	24 (82.8)		

Legend: *=McNemar test is statistically significant if $p < 0.05$.

Table 3. Bivariate analysis between confounding variables and mortality

Variable	Case group	Control group	P	OR (CI95%)
Primary diagnosis, n (%)				
Surgical	11 (21.6)	6 (11.8)	0.227	2.67 (0.64-15.61)
Non-surgical	40 (78.4)	45 (88.2)		
Severity of disease, n (%)				
Very severe (PELOD scores >22)	8 (15.7)	0 (0.0)	0.008*	- (1.71-∞)
Severe (PELOD scores ≤22)	43 (84.3)	51 (100.0)		
The use of mechanical ventilator, n (%)				
Yes	50 (98.1)	22 (43.1)	0.000*	- (7.10-∞)
No	1 (2.0)	29 (56.9)		
Nutritional status, n (%)				
Malnutrition	30 (58.8)	15 (29.4)	0.004*	4.00 (1.46-13.64)
Good	21 (41.2)	36 (70.6)		
HAP, n (%)				
Yes	10 (19.6)	2 (3.9)	0.022*	9.0 (1.25-394.48)
No	41 (80.4)	49 (96.1)		
VAP, n (%)				
Yes	12 (23.5)	2 (3.9)	0.013*	6.00 (1.34-55.19)
No	39 (76.5)	49 (96.1)		
CAUTI, n (%)				
Yes	12 (23.5)	6 (11.8)	0.179	2.50 (0.72-10.92)
No	39 (76.5)	45 (88.2)		
SSI, n (%)				
Yes	3 (5.9)	0 (0.0)	0.250	- (0.41-∞)
No	48 (94.1)	51 (100.0)		

Legend: *=McNemar test is statistically significant if $p < 0.05$.

Table 4. Multivariate analysis of variables that affect mortality

Variable	P	OR (CI 95%)
Parenteral route of initial caloric administration	0.004*	36.05 (3.22-404.13)
Lack of caloric achievement on day 2	0.548	2.18 (0.17-27.89)
Lack of caloric achievement on day 3	0.592	0.39 (0.01-11.63)
Lack of caloric achievement on day 4	0.194	16.57 (0.24-1145.15)
HAP	0.995	2255000000 (0-∞)
VAP	0.111	8.19 (0.62-108.75)
CAUTI	0.682	1.72 (0.13-13.03)
Malnutrition	0.003*	9.04 (2.09-39.19)
Surgical category as primary diagnosis	0.275	0.08 (0.001-7.31)

Legend: *=conditional logistic regression test with stepwise method statistically significant if $p < 0.05$.

Table 5. Stratified analysis for initial route of caloric administration and mortality by groups of nutritional status and severity of disease

			Case group		Control group		P	OR (CI 95%)
			N	%	N	%		
Nutritional status	Good	Parenteral	9	42.9	2	5.6	0.001	12.75 (2.1-130.6)
		Enteral	12	57.1	34	94.4		
	Malnutrition	Parenteral	5	16.7	0	0.0	0.094	∞ (0.7-∞)
		Enteral	25	83.3	15	100.0		
Severity of disease	Severe (PELOD scores ≤ 22)	Parenteral	13	30.2	2	3.9	0.001	10.62 (2.1-100.9)
		Enteral	30	69.8	49	96.1		
	Very severe (PELOD scores > 22)	Parenteral	1	12.5	0	0.0	-	
		Enteral	7	87.5	0	0.0		

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