RESEARCH

Enteral Nutrition Tolerability Assessment in Septic Shock Patients in The ICU of RSUP H. Adam Malik Medan

Aulia Kamal Ansari[*], Andriamuri Primaputra Lubis[✉**], Rommy Fransiscus Nadeak[**]

[*]Master of Clinical Medicine Study Program/Anesthesiology and Intensive Care Study Program, Faculty of Medicine, Universitas Sumatera Utara/RSUP H. Adam Malik, Medan, Indonesia
[**]Department of Anesthesiology and Intensive Care, Faculty of Medicine, Universitas Sumatera Utara /RSUP H. Adam Malik, Medan, Indonesia

[✉]Correspondence: andriamuri@usu.ac.id

ABSTRACT
Background: Enteral nutrition is recommended within 24 to 48 hours after intensive care unit (ICU) admission when resuscitation and hemodynamic stability have been achieved. This study aims to determine the tolerability of enteral nutrition in septic shock patients in the ICU.
Objective: To determine the tolerability of enteral nutrition in septic shock patients in the ICU of RSUP H. Adam Malik Medan.
Methods: This study is a retrospective observational study, which was conducted in the ICU of the RSUP H. Adam Malik Medan by taking patient data from January to December 2022. The samples were septic shock patients who were admitted to the ICU using mechanical ventilation and vasopressors with a length of treatment of more than 48 hours. Data was collected on the time required for enteral nutrition administration, as well as assessing patient tolerability (presence of vomiting, residuals, and incidence of ileus). Other assessments included length of stay and mortality rate.
Result: This study consisted of 47 samples, with 23 male (48.9%) and 24 female (51.1%) samples. Based on the underlying disease, 40.4% of the samples were diagnosed with pneumonia. In the tolerability of enteral nutrition, 83% of the samples were tolerant of early enteral nutrition, but with a high mortality rate of 89.4%. The initiation time of enteral nutrition in patients was 4.94 ± 1.79 hours (p=0.001). The average hospital stay for sepsis patients was 7.30 ± 6.55 days (p=0.001).
Conclusion: Most sepsis and septic shock patients in the ICU are tolerant of early enteral nutrition <24 hours, but it does not reduce mortality.

Keywords: anesthesia; enteral nutrition; ICU; sepsis; tolerability

INTRODUCTION

Sepsis is a life-threatening condition caused by dysregulation of the body's response to an infection, resulting in organ dysfunction. Septic shock is a circulatory, cellular, and metabolic abnormality in sepsis patients, as well as hypotension requiring vasopressors which is associated with tissue hypoperfusion (lactate > 2 mmol/L).[1]

Enteral nutrition is recommended within 24 to 48 hours of intensive care unit (ICU) admission when resuscitation and hemodynamic stability have been achieved. The Society of Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition recommend delaying enteral nutrition in patients who have a mean arterial pressure of less than 50 mmHg and in patients who require initiation or escalation of vasopressors.[2]

A study conducted at New York University Langone Medical Center on septic shock patients with mechanical ventilators and vasopressors found that early enteral nutrition was tolerated and safe in septic shock patients who received adequate fluid resuscitation and received norepinephrine doses <0.14 ug/kg/min.[3] Another study that assessed the tolerability and safety of enteral nutrition in critically ill patients (48% septic shock) who received intravenous vasopressor therapy found that 74.9% of patients tolerated enteral nutrition and intolerant patients received the use of norepinephrine at doses up to 12.5 ug/min or patients received dopamine and vasopressin simultaneously. Adverse events included increased lactate serum, increased gastric residue, vomiting, positive findings on renal/ureteral/bladder radiographs, and bowel ischemia/perforation.[4]

METHODS

This study was an observational study conducted retrospectively. The study aimed to determine the tolerability of enteral nutrition in septic shock patients in the ICU of RSUP H. Adam Malik Medan. After calculating the sample, a minimum sample of 47 samples was obtained.

This study began after obtaining approval from the Ethics Committee of the Universitas Sumatera Utara and research permission from the Research and Development section of RSUP H. Adam Malik Medan, and patients who fulfilled the inclusion and exclusion criteria were collected from medical records. Patient data were collected using a data collection form by the researcher, and there was no intervention treatment from the researcher to the patient as a research sample. Research data were collected simultaneously with patient clinical data according to medical records. The data collected included name, age, gender, diagnosis, comorbidities, laboratory results, time of enteral nutrition, events that occurred during enteral nutrition (gastric residue, emesis, intestinal paralysis, or intestinal ischemia/perforation), length of stay in the ICU, and mortality. After obtaining the data, the tolerability of enteral nutrition was assessed. Tolerability of enteral nutrition was stated if there were no signs/symptoms such as vomiting, gastric residue >250 ml, or intestinal paralysis reports. However, if any of these events were encountered, it was declared as enteral nutrition intolerance. The tolerant and intolerant groups will be statistically tested to assess the significance between data variables, and other data will be tabulated and analyzed by the researcher.

RESULTS

In the distribution of samples based on the underlying diagnosis of sepsis or septic shock, 20 samples (42.5%) were diagnosed with pneumonia, 6 samples (12.7%) with a diagnosis of acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD) and pulmonary tuberculosis (TB). There were 5 samples (10.6%) each with a base diagnosis of diabetes mellitus and neurological disorders (meningitis, tetanus, Guillain-Barre Syndrome, and space occupying lesion (SOL); 4 samples (8.5%) with uremic encephalopathy, and the remaining patients with diagnoses of gastrointestinal diseases such as cholangitis, bile duct stone and hepatic cysts (6.4%), cardiovascular diseases (4.25%) and other causes such as preeclampsia and nasopharyngeal carcinoma.

Table 1. Frequency distribution based on gender

Variable	Total (n=47)
Gender, n (%)	
Male	23 (48.9)
Female	24 (51.1)

Table 2. Frequency distribution based on diagnosis

Variable	Total (n=47)
Diagnosis, n (%)	
Pneumonia	20 (42.5)
Other lung diseases (ARDS, COPD, TB)	6 (12.7)
Diabetes Mellitus (Diabetic Ulcer, Diabetic Gangrene)	5 (10.6)
Neurology Disorders (Meningitis, Tetanus, GBS, SOL)	5 (10.6)
Uremic Encephalopathy	4 (8.5)
Gastrointestinal disorders (Cholangitis, Choledocholithiasis, Liver Cyst)	3 (14.9)
Cardiovascular disorders (CHF, Lung Edema)	2 (4.25)
Others (Severe Preeclampsia, Nasopharyngeal Carcinoma)	2 (4.25)

Patient tolerance to enteral feeding is divided into tolerant and intolerant which is assessed by the presence or absence of vomiting incidents, the amount of residue, and peristalsis in patients after receiving the diet within 24 hours. In this study, 39 samples were tolerant (83%) while the remaining 8 samples were intolerant (17%) to early enteral nutrition.

Table 3. Frequency distribution based on tolerability

Variable	Total (n=47)
Tolerability, n (%)	
Tolerant	39 (83.0)
Intolerant	8 (17.0)

Mortality of the study sample refers to the condition of the patient at the time of discharge from the ICU of RSUP H. Adam Malik Medan which consists of discharge from the ICU and then moving to the inpatient ward or discharge from the ICU with a state of death. There were 42 patients who died (89.4%) and 5 patients were discharged from the ICU and moved to the inpatient ward (10.6%).

Table 4. Frequency distribution of tolerability

Variable	Total (n=47)
Tolerability, n (%)	
Vomiting	0/47
Residue > 250 cc	8/47
Paralysis	0/47

Based on the nutritional tolerability assessment, the cause of enteral nutrition intolerance found was the presence of residue in 8 samples. Signs of intolerance due to vomiting and paralysis were not found.

Table 5. Frequency distribution based on mortality

Variable	Total (n=47)
Mortality, n (%)	
Yes	42 (89.4)
No	5 (10.6)

The youngest age in this study sample was 23 years, with a total of 1 person (2.1%) and the oldest age was 88 years old, with also a total of 1 person (2.1%) with an average age of 54.3 years. The shortest length of stay (LOS) in the ICU of RSUP H. Adam Malik Medan was 2 days in 6 samples (12.8%) and the longest LOS was 35 days in 1 sample (2.1%) with an average LOS of 7.3 ± 6.55 days and p value of 0.001, which indicated that the data are not normally distributed.

Based on the patient's hemodynamics at the time of enteral nutrition, the samples had an average mean arterial pressure (MAP) of 83.31 ± 14.44 mmHg, with p = 0.255, which indicated that the data was normally distributed. Meanwhile, the heart rate of the samples had a mean of 97.93 ± 16.24 times/minute, with p = 0.462, and based on the assessment of central venous pressure (CVP) the samples had an average of 7.01 ± 1.98 cmH_2O with a value of p = 0.322. The dose of vasopressors used during enteral nutrition had a mean of 0.4 ± 0.2 mcg /kg/hour, with a value of p = 0.001, indicating that it was not distributed normally.

Initiation time refers to the time from the patient's admission to the ICU of RSUP H. Adam Malik Medan until the patient receives an enteral diet. The shortest initiation time was 2 hours and was received by 1 sample (2.1%) while the longest initiation time was 8 hours which was received by 9 samples (19.1%) with an average initiation time of 4.9 ± 1.79 hours. The lowest albumin level in this study sample was 1.5 gr/dl while the highest albumin level was 4.2 gr/dl with a mean albumin level of 2.7 gr/dl.

Body mass index (BMI) in this study sample was measured before the patient was given a diet in the ICU of RSUP H. Adam Malik Medan. The lowest BMI value in this study sample was 20.4 kg/m2 and the highest was 27.5 kg/m2, each of which was found in 1 sample (2.1%) with a mean BMI of 23.6 ± 1.45 kg/m2. With a p value = 0.583, the data is said to be normally distributed.

Table 6. Frequency distribution based on age, LOS, initiation time, albumin, and BMI

Variable	Minimum	Maximum	Mean ±SD	Nilai-p
Age (years)	23	88	54.36 ± 14.4	0.108
Mean Arterial Pressure (MAP)	60	119	83.31 ± 14.44	0.255
Heart Rate	72	133	97.93 ± 16.24	0.462
CVP (mmHg)	3.5	11.2	7.01 ± 1.98	0.322
Vasopressor (mcg/kg/hour)	0.1	0.9	0.4 ± 0.2	0.001
Length of stay (days)	2	35	7.30 ± 6.55	0.001
Initiation time (hours)	2	8	4.94 ± 1.79	0.001
Albumin (gr/dl)	1.50	4.20	2.71 ± 0.56	0.894
BMI (kg/m^2)	20.40	27.50	23.63 ± 1.45	0.583
Residue (cc)	10	350	106 ± 95	0.001

DISCUSSION

Sepsis which requires treatment in ICU is characterized by an acute catabolic response that causes rapid mobilization of energy reserves as muscle, glycogen, and lipid reserves are broken down to drive glucose production. This contributes to a rapid loss of lean body mass that contributes to muscle wasting, weakness, and loss of physical function. It is known that nutritional therapy in patients with sepsis differs from the standard nutritional approach in critically ill patients. Medical nutrition therapy (MNT) includes various components such as timing of administration, route of administration (enteral and parenteral), amount and composition of macronutrients and micronutrients. Medical nutrition therapy is expected to distinctly interfere with endogenous metabolic responses depending on the phase of the disease and the nature of the triggering homeostasis disturbance and thus likely to influence clinical outcomes.[5,6,7]

Based on the recommendations of the European Society for Clinical Nutrition and Metabolism (ESPEN), nutritional therapy should be considered for all patients undergoing treatment in the ICU, especially those for more than 48 hours. Any critical patient admitted to the ICU for more than 48 hours should be considered at risk of malnutrition. Patients are malnourished due to severe loss of appetite and weight loss leading to a reduction in body mass whether with comorbidities or not and they will usually receive nutritional support. That is why nutritional interventions need to be carefully planned.[8]

In planning, an oral diet should be preferred over enteral or parenteral nutrition in critically ill patients who are still able to eat orally. If oral intake is not possible, early enteral nutrition (within 48 hours) should be practiced over parenteral nutrition. When oral and enteral diets are not feasible, parenteral nutrition can be given within 3-7 days.[8] Enteral nutrition is safe and appropriate in patients with mild or moderate paralytic ileus, as long as the patient's hemodynamic status is stable. The rate of achieving the target amount of enteral nutrition within 72 hours is reported to be 30 to 85%, when enteral nutrition is started after hemodynamic stabilization, even before the presence of peristaltic sounds.

On administration, enteral nutrition should be delayed until the patient is fully resuscitated, and the enteral route should not be used if there is hemodynamic compromise or instability. These recommendations apply to patients with hypotension and the use of vasopressor support or inotropes. In patients with stable, low-dose vasopressor support, enteral nutrition can be given with caution, but should be discontinued immediately, if there are early signs of intestinal ischemia (abdominal distension, symptoms of paralytic ileus, vomiting/increased gastric residue), or acid-base disturbances including lactic acidosis). Enteral nutrition should also be delayed in patients with septic shock until resuscitation is complete.[7] In our study, it was seen that patients who used vasopressor support could be given enteral nutrition from the beginning due to stable hemodynamics, with a mean MAP of 83.31±14.44 mmHg.

In our study, 83% of the samples were tolerant to early enteral nutrition. Despite enteral nutrition, some gastrointestinal disorders and symptoms can still occur in critical care patients and may be triggered by several factors, including pre-onset illness, general condition, metabolic state, ventilator use, and medications administered. Gastrointestinal distress may be associated with intestinal intolerance during enteral nutrition. The mechanism of gastrointestinal distress in critically ill or postoperative patients can be classified as mucosal barrier failure, decreased peristalsis and atrophy of intestinal mucosa, decreased intestinal lymphatic tissue and so on.[9]

In addition, this study also found that the time required to start enteral nutrition was less than 48 hours (4.94 hours; p=0.001). This is in line with several studies, including a study by *Jiang Yongpo et al*, which found that enteral nutrition <24 hours is associated with a better prognosis in patients with sepsis or septic shock, and enteral nutrition can be used as an independent prognostic factor for sepsis patients. In another meta-analysis study, it was found that early enteral nutrition, within 24 hours, had no significant difference in mortality compared to parenteral nutrition. This is in line with our results, which showed that 89.4% of samples with septic shock who received enteral nutrition under 24 hours died within 28 days of monitoring. A study conducted at New York University Langone Medical Center on septic shock patients with mechanical ventilators and vasopressors found that early enteral nutrition was tolerated and safe in septic shock patients who received adequate fluid resuscitation and norepinephrine doses <0.14 ug/kg/min.[10]

Another study that assessed the tolerability and safety of enteral nutrition in critically ill patients (48% in septic shock) who received intravenous vasopressor therapy found that 74,9% of patients tolerated enteral nutrition and intolerant patients received the use of norepinephrine at a dose up to 12.5 ug/min or patients received dopamine and vasopressin simultaneously.[10]

Research conducted at the Hasan Sadikin Hospital Bandung regarding the timing of initiation and fulfillment of enteral nutrition intake in patients using mechanical ventilation found that 38 patients received enteral nutrition <48 hours and as many as 6 patients were intolerant with high gastric residue.[11]

This may occur because in some clinical studies (trauma, postoperative patients) is known that enteral nutrition can maintain intestinal mucosal integrity and reduce intestinal permeability and, together, can enhance intestinal barrier immunity, and prevent bacterial and endotoxin translocation to reduce the incidence of secondary infections. However, intestinal dysfunction occurs in patients with sepsis; translocation of bacteria and endotoxins is itself one of the mechanisms of sepsis. Therefore, it will not help reduce the incidence of new infections.[9,12]

In our study, the cause of sepsis was based on the diagnosis of pneumonia (42.5%). Sepsis is a major risk factor for the development of acute hypoxemic respiratory failure especially in the presence of shock. Other factors contributing to the development of respiratory failure include young age, higher APACHE II score, pulmonary source of infection, acute pancreatitis, and acute abdomen. In sepsis, acute respiratory failure remains associated with worse outcomes. Early identification and intervention of patients at risk of acute respiratory failure is feasible. In sepsis-associated respiratory failure, early liberal and late conservative fluid strategies are associated with better outcomes.[13] In the world quoted from World Sepsis Day, 19.7% of sepsis cases caused by pneumonia experience death. in Indonesia, 60% of sepsis cases are caused by pneumonia.[13]

In the intensive care setting, serum albumin has long been a predictor of poor clinical outcome although it is also a reflection of acute phase response. In 83 critically ill patients, a decrease in plasma albumin concentration corresponds to an increase in pulmonary vascular permeability regardless of the underlying disease and fluid status of the patient. The relationship between hypoalbuminemia and poor outcome appeared to be independent of nutritional status and inflammatory processes. Every 10 g/L decrease in serum albumin concentration significantly increases the likelihood of death by 137%.[14] This may also be the cause of the high mortality rate in the study sample, as the mean serum albumin of the study sample was 2.71 gr/dL.

Guidelines recommend that enteral nutrition be quantitatively adequate in terms of nutrient content, in addition to initiating earlier administration. Patients should get 50-65% of energy requirements within the first 3 days of hospitalization and should meet all necessary goals within the first 7 days. In critical care patients, low caloric intake during the first week in the ICU is associated with a higher risk of mortality, while negative energy balance is associated with increased infections, prolonged time on mechanical ventilation, and LOS in the ICU. In contrast, time on mechanical ventilation and length of stay were not associated with low caloric intake during the first week of ICU stay.[15]

There were some limitations in this study. First, this study was retrospective. This study could only look at the description of the sepsis samples taken in the study, so it could not assess the relationship between nutrition and other outcomes, such as mortality rate, length of stay, use of vasopressors, and changes in albumin levels. Secondly, in the case of enteral nutrition, the components of the nutrition given to the patients admitted to the ICU were unknown, so the uniformity of the nutrition was unknown. Further research is needed to improve this study.

CONCLUSION

Most sepsis and septic shock patients in the ICU are tolerant of early enteral nutrition <24 hours, but it does not reduce mortality

REFERENCES

1. S Kong G, Lin K, Hu Y. Using machine learning methods to predict in-hospital mortality of sepsis patients in the ICU. BMC medical informatics and decision making. 2020 Dec;20:1-0.
2. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, Colombara DV, Ikuta KS, Kissoon N, Finfer S, Fleischmann-Struzek C. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. The Lancet. 2020 Jan 18;395(10219):200-11.
3. Patel JJ, Rice T, Heyland DK. Safety and outcomes of early enteral nutrition in circulatory shock. Journal of Parenteral and Enteral Nutrition. 2020 Jul;44(5):779-84.
4. Merchan C, Altshuler D, Aberle C, Papadopoulos J, Schwartz D. Tolerability of enteral nutrition in mechanically ventilated patients with septic shock who require vasopressors. Journal of Intensive Care Medicine. 2017 Oct;32(9):540-6.
5. Wischmeyer PE. Nutrition therapy in sepsis. Critical care clinics. 2018 Jan 1;34(1):107-25.
6. Cha JK, Kim HS, Kim EJ, Lee ES, Lee JH, Song IA. Effect of early nutritional support on clinical outcomes of critically ill patients with sepsis and septic shock: A single-center retrospective study. Nutrients. 2022;14:2318
7. Kott M, Hartl W, Elke G. Enteral vs. parenteral nutrition in septic shock: are they equivalent?. Co-critical care. 2019;25(4): 340-348
8. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, Hiesmayr M, Mayer K, Montejo JC, Pichard C, Preiser JC. ESPEN guideline on clinical nutrition in the intensive care unit. Clinical nutrition. 2019 Feb 1;38(1):48-79.
9. Tatsumi H. Enteral tolerance in critically ill patients. Journal of intensive care. 2019 Dec;7(1):1-0.

10. Merchan C, Altshuler D, Aberle C, Papadopoulos J, Schwartz D. Tolerability of enteral nutrition in mechanically ventilated patients with septic shock who require vasopressors. Journal of Intensive Care Medicine. 2017 Oct;32(9):540-6.
11. Irawati D, Suwarman IS. Waktu Inisiasi dan Pemenuhan Asupan Nutrisi Enteral pada Pasien yang Menggunakan Ventilasi Mekanik di Intensive Care Unit (ICU) Rumah Sakit Dr. Hasan Sadikin Bandung. 2020.
12. Peng L, Wu LG, Li B, et al. Early enteral nutrition improves intestinal immune barrier in a rat model of severe acute pancreatitis. J Hepatobiliary Pancreat Sci 2016;23:681-7. Peng L, Wu LG, Li B, et al. Early enteral nutrition improves intestinal immune barrier in a rat model of severe acute pancreatitis. J Hepatobiliary Pancreat Sci 2016;23:681-7.
13. Hatman FA, Semedi BP, Budiono B. Analisis Faktor Risiko terhadap Lama Perawatan Pasien Sepsis yang Meninggal di Ruang Perawatan Intensif RSUD Dr. Soetomo Surabaya. JAI (Jurnal Anestesiologi Indonesia). 2021;13(2):78-87.
14. Takegawa R, Kabata D, Shimizu K, Hisano A, Ogura H, et al. Serum albumin as a risk factor for death in patients with prolonged sepsis. An observational study. Journal of Critical Care. 2019;51:139-144
15. Pasinato V, Berbigier M, Rubin B, Castro K, Moraes R, Perry ID. Enteral nutritional therapy in septic patients in the intensive care unit: compliance with nutritional guidelines for critically ill patients. Rev Bras Ter Intensive. 2013;25(1):17-24