Journal of Society Medicine
Research & Review Articles on Diseases
Journal of Society Medicine. 2022; 1(1)

Comparison of Pre-Loading Fluid With Norepinephrine Toward Mean Arterial Pressure (MAP) In Sepsis Patients In Intensive Care Unit (ICU) of Haji Adam Malik General Hospital, Medan

Rendi Sidiq[1], Bastian Lubis[1], Yutu Solihat[1]
[1]*Department of Anesthesiology and Intensive Care, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia*

***Corresponding Author**: Rendi Sidiq, E-mail: rendi@gmail.com

ARTICLE INFO

Article history:
Received
25 September 2022

Accepted
11 October 2022

Manuscript ID:
JSOCMED-221011-6

Checked for Plagiarism: Yes

Language Editor:
Hendi Ishadi

Editor-Chief:
Prof. dr. Aznan Lelo, PhD, Sp.FK

ABSTRACT

Introduction: Sepsis is a life-threatening organ dysfunction caused by dysregulation of the host response to infection. Sepsis and septic shock are major health problems, affecting millions of people worldwide each year and killing one in six people affected. Early identification and appropriate management in the early hours after the development of sepsis improves the patient's prognosis. Surviving Sepsis Campaign (SSC) 2021 recommends a fluid dose of 30mL/kgBW, but there are many studies stating that there is no difference in patient outcomes when we resuscitate patients with 10 or 20 mL/kgBW fluids. Norepinephrine is considered as the safest and most potent vasopressor agents than others.
Methods: This study used a double-blind randomized clinical trial (RCT) design to assess MAP in sepsis patients in intensive care unit (ICU) of Haji Adam Malik General Hospital ,Medan.
Results: There were more male (56.5%), than female (43.5%). In our study, administration of 10mL/kg and 20mL/kg fluid bolus with vasopressor resulted in increased MAP, and the differences were statistically significant ($p < 0.05$). Administration of 10 mL/kg fluid gave higher MAP values than the other groups, could be a consideration in choosing fluid in order to avoid fluid overload.
Conclusion: There is a significant comparison in the ratio of norepinephrine pre-loading fluid toward MAP in sepsis patients. Comparison of the mean MAP value at 15, 20, 25 minutes was the highest in the 10 mL/KgBW group. Meanwhile, the lowest MAP was found in 30mL/KgBW the group.

Keywords Norepinephrine, Intensive Care Unit, Pre-Loading Fluid

INTRODUCTION

Infection is a disease caused by pathogenic microbes that can cause tissue damage and interfere with organ's function. If it is not treated quickly and appropriately, it can spread into the bloodstream and cause complications, namely sepsis [1]. Sepsis is one of the most important medical problems, as the course of sepsis can lead to septic shock and could increase the risk of death significantly [2].

The incidences of sepsis and severe sepsis have increased over the last decade from approximately 600,000 to more than 1,000,000 hospitalizations per year from 2000 to 2008. Mortality of patients with sepsis have decreased due to advances in sepsis management provided by the Surviving Sepsis Campaign (SSC). The United States nationwide inpatient sample (NIS) from 2009 to 2012 showed the decrease of mortality rate from

16.5% to 13.8%. However, severe sepsis continues to be the most common cause of death in hospitalized patients [3].

Indonesia is a country with a high sepsis mortality rate around 44.5% in 2009 from all cases of sepsis and severe sepsis including 10.9% from intensive care patients. The data in the Cipto Mangunkusumo General Hospital show the number of patients treated with sepsis is 10.3% of the total patients treated in the internal medicine room. Sepsis was the leading cause of death for 3 years, from 2009 to 2011. This figure increased from 49% in 2009 to 55% in 2011 [4].

Sepsis is a medical emergency, so fluid should be given as soon as possible after a patient is suspected of having sepsis with/or without hypotension and increase in lactate levels. The most common recommendation for intravenous fluid administration is at least 30ml/kg of crystalloid fluids [5]. Patients in modern early goal-directed therapy (EGDT) and usual care trials received an average of 27 mL/kg fluid before randomization, slightly less than the recommendation by current SSC guideline [6].

Brown and Semler recommended a slightly more conservative initial bolus of 20 mL/kg intravenous fluid for patients with septic shock, given the potential danger of fluid resuscitation-induced volume overload. Careful monitoring of the patient's respiratory function and hemodynamics is necessary because one-third to one-half of patients will develop persistent hypotension after initial fluid bolus administration, which requires clinicians to weigh the risks and benefits of further fluid administration or the initiation of vasopressors [7]. Jozwiak et al recently proposed initiating fluid administration with an infusion of 10 mL/kg in the first 30 to 60 minutes while monitoring the patient closely [8].

If shock persists after 15-30 minutes of fluid resuscitation, no additional fluid are given. If fluid boluses fail to maintain adequate organ perfusion and arterial pressure, vasopressor agents should be administered immediately to maintain the mean arterial pressure (MAP) ≥ 65 mmHg [7]. For adults with septic shock, the 2021 SSC guidelines recommend the use of norepinephrine as a first-line agent over other vasopressors [9].

Norepinephrine is a potent α-1 and β-1 adrenergic receptor agonist, which causes vasoconstriction and increases MAP with minimal effect on heart rate. Norepinephrine is more potent than dopamine as a vasoconstrictor [9]. Studies comparing the impact of 40 mL/kg fluid over 15 minutes followed by dopamine and further titration of therapy versus 20 mL/kg over 20 minutes to a maximum of 60 mL/kg for 1 hour followed by dopamine (control protocol) on septic shock do not show any differences in overall mortality, speed of shock resolution, or incidence of complications between groups [10]. This study was conducted to determine the comparison of MAP after pre-loading fluid of 10, 20, and 30 mL/kgBW with norepinephrine in sepsis patients in the intensive care unit (ICU) of Haji Adam Malik General Hospital.

METHOD

This study used a double blind randomized clinical trial (RCT) design, meaning that both research subjects and researchers did not know about the treatment or intervention given. The study was conducted in the ICU of Haji Adam Malik General Hospital Medan after passing the ethical clearance and until the number of samples was met. This research started from the middle of January 1 until February 28, 2022. The study population was patients diagnosed with sepsis in the ICU General Hospital Haji Adam Malik Medan with SOFA score >2. The research samples were the research population that met the inclusion and exclusion criteria. Samples were collected using consecutive sampling method, which is looking for patients who met the inclusion and exclusion criteria until the required number of samples was met. The inclusion criteria for our study were patients aging 21-64 years with a sepsis diagnosis, had SOFA score >2 in the ICU, and willing to participate in the study by signing a consent letter. While the exclusion criteria were patients who were uncooperative or refused to participate in the study, patients with a history of hypersensitivity to norepinephrine, and women who were pregnant.

The minimum total research subjects of this study was 60 subjects who met the inclusion and exclusion criteria. After obtaining approval from the Ethics Committee of the Faculty of Medicine, University of North Sumatra, research samples were taken in the ICU of Haji Adam Malik General Hospital Medan. The research subjects were then randomized into 3 groups, the 10cc/kgBW group, 20cc/kgBW group, and 30cc/kgBW group. Next, samples were collected until the number of samples is sufficient, adjusting to the inclusion and exclusion criteria, and taken using the consecutive sampling method. The MAP results were recorded 15, 20 and 25 minutes after fluid resuscitation.

Patients underwent treatment during the study in the ICU. Research subjects were assessed according to secondary data at the time of initial treatment in the ICU. Patients' identities were recorded and MAPs were assessed using MAP score table after fluid and 0.05 µg/kg/min norepinephrine administration were done in each group. Research subjects were assessed with a score of 1, 2, to 3 in all three domains. All scores from each domain were then summed. All data collected were tabulated and analyzed with unpaired T test for parametric data and Mann-Whitney test using SPSS version 26. Characteristics of research subjects consisting of identity, MAP score, blood pressure, pulse, and assessment were statistically analyzed and presented in a frequency distribution table. The results of the bivariate analysis to see differences in MAP will be carried out using an unpaired T test with SPSS version 26.

RESULTS

A total of 62 samples who met the inclusion and exclusion criteria were included in the study. Characteristics of the subjects in this study can be distinguished by age and gender.

The results can be seen in Table 1. In group 1, the largest sample age was in the 61-64 year age group with a total of 6 samples (30%), and the least was in the 21-25 year age group with a total of 0 sample (0 %); in group 2 the most sample in age category was also in the 61-64 years group with a total of 8 samples (38%) and the least were in the 21-25 years, 26-35 years and 56-60 years group with a total of 2 samples (9.5%) each; while in group 3 the most samples in age categories was in the group 46-55 years with a total of 7 samples (33.3%) and the least were in the group 21-25 years, 26-35 years and 56-60 years with a total of 2 samples (9,5%) each. In this study, there were more male (56.5%) than female (43.5%).

Table 1. Patients characteristics

Characteristics	Sample Group						Total	
	Group 1 10cc/kgBW		Group 2 20cc/kgBW		Group 3 30cc/kgBW			
Age	n	%	n	%	n	%	n	%
21-25 years	0	0	2	9,5	2	9,5	4	6,5
26-35 years	2	10	2	9,5	2	9,5	6	9,7
36-45 years	4	20	3	14,4	3	14,4	10	16,1
46-55 years	7	35	4	19,1	7	33,3	18	29
56-60 years	1	5	2	9,5	2	9,5	5	8,1
61-64 years	6	30	8	38	5	23,8	19	30,6
Total	20	100	21	100	21	100	62	100
Gender								
Male	11	55	10	47,6	14	66,7	35	56,5
Female	9	45	11	52,4	7	33,3	27	43,5
Total	20	100	21	100	21	100	62	100

Based on the Kolmogorov-Smirnov normality test (Table 2), it is shown that HR variables were normally distributed and other variables were not normally distributed. The data were declared normally distributed if the p-value of the normality test was > 0.05 and was declared not normally distributed if the p-value of the normality test was <0.05. Data which were normally distributed were interpreted with mean and standard deviation while those not normally distributed were interpreted with median, minimum, and maximum.

Table 2. Results of descriptive analysis and data normality

Data type	Mean	±SD	Median	Min	Max	P *value*
Age, years	51,77	14,35	54	21	64	0,031
Height, cm	161,84	7,16	162	130	172	0,006
Sistole, mmHg	114,07	25,98	109	80	180	0,000
Diastole, mmHg	66,75	18,94	67	37	115	0,001
HR, bpm	103,03	21,6	106	22	149	0,200
RR, rpm	23,34	10,37	22	14	88	0,000
Temperature, ^{O}C	37,36	0,8	37,2	36,6	38,8	0,000
MAP Group 1, mmHg	98,38	16,16	98,22	64	135,67	0,967
MAP Group 2, mmHg	71,97	13,78	64,67	58	100	0,001
MAP Group 3, mmHg	76,39	17,10	67,34	60,67	115,67	0,002

Analysis of the Difference Test Between Each Sample Group

Based on Table 3, there was a significant difference between group 1 and group 2 at each MAP examination (p<0.001). It is also known that there was a significant difference between group 1 and group 3 at each MAP examination (p<0.001). Lastly, there was no significant difference between group 2 and group 3 (p>0.05).

Table 3. Results of analysis between each treatment group

Data Type	**Route**	**p-value**
Group 1 – Group 2	MAP 15	0,000
	MAP 20	0,000
	MAP 25	0,000
Group 1 – Group 3	MAP 15	0,000
	MAP 20	0,000
	MAP 25	0,000
Group 2 – Group 3	MAP 15	0,561
	MAP 20	0,800
	MAP 25	0,850

Based on Table 4, there was a significant difference between all groups in each measurement (p<0.001).

Table 4. Results of overall data difference test based on time

Data Type	**Mean**	**± SD**	**P-value**
MAP15	76,36	18,28	0,000
MAP20	78,85	18,78	0,000
MAP25	81,23	18,85	0,000

DISCUSSION

In our study, most patients aged more than 60 years with a median age of 54 (21 – 64) years. In general, the incidence of sepsis increases with age. This is because older age is associated with worsening of the immune system and organ functions, as well as many comorbid conditions [11]. The elderly also require higher blood pressure to maintain adequate perfusion due to increased arterial wall stiffness [12]. In addition, because of the blunted heart rate response, cardiac output is primarily dependent on the filling pressure of the heart by adequate preload [13]. In one study, it was shown that elderly patients in the emergency department with suspected infection, at systolic blood pressure <140 mmHg were associated with higher mortality. Thus, older patients may receive insufficient fluid volume to achieve adequate perfusion, which may affect patient outcome [14].

There were more male (56.5%) than female subjects (43.5%) in this study. Females have been reported to experience sepsis less frequently and have a lower risk of mortality from sepsis than males. A previous study by Nasir et al suggested that the higher mortality in men may be related to differences in the rate of respiratory tract infection and plasma IL-6 levels between the two genders [15].

Our subjects had a median height of 162 (130 – 172) cm. This condition is similar to a previous study by Garcı´a et al (2015) which investigated the effect of fluid administration on arterial load in critically ill patients with septic shock. Systolic and diastolic blood pressure in our study subjects before fluid resuscitation had a median of 109 mmHg (80 – 180 mmHg) and 67 mmHg (37 – 115 mmHg) respectively. Our subjects' heart rate had a mean of 103.03 ± 21.6 times per minute and respiratory rate median of 22 (14 – 88) breaths per minute. In our study, patients were not grouped based on comorbid cardiovascular and respiratory organs or the source of infection causing sepsis. Patients with sepsis, especially those in the ICU who fall into a state of shock, have comorbid conditions such as coronary heart disease, congestive heart failure, hypertension, and chronic lung disease [16].

A previous study conducted by Garcı´a et al (2015) on 81 critically ill patients with septic shock in the ICU, which investigated the effect of fluid administration on arterial load and its components (mean arterial pressure, systemic vascular resistance, cardiac output, stroke volume, and arterial pulse pressure), classified the recording of hemodynamic changes into preload responders and non-responders and pressure responders and non-responders. The preload responder group were those who experienced an increase of >10% in cardiac output after fluid administration. Meanwhile, the pressure responder group were those who experienced an increase >10% in MAP. The speed of fluid administration given is 500 cc of normal saline in 30 minutes. In their study, the median systolic and diastolic blood pressures in the preload responder group were 106 (98 – 124) mmHg and 54 (46 – 64) mmHg. These conditions are more or less in line with the conditions in our study [17].

MAP values in our study were measured 15, 20, and 25 minutes after crystalloid resuscitation and 0.05 µg/kg/min norepinephrine administration. MAP results in 15, 20, and 25 minutes after fluid administration had a median of 64.3 (55 – 116); 67 (57 – 116); and 73 (60 – 117) respectively. In general, there was an increase in MAP at 15, 20 and 25 minutes after fluid resuscitation regardless of the amount of fluid given. In previous studies, there was a 6% (2 – 14%) increase in MAP of all subjects and a 9% (1 – 18%) increase in MAP of the preload responders group (who experienced an increase in cardiac output >10%) after administration of fluid expansion. In that study, a 10% increase in MAP (pressure responder) occurred in 36% of subjects, and in the preload responder group only 44% of patients were pressure responders [17].

Administration of fluid expansion was associated with a significant reduction in arterial load (including systemic vascular resistance (SVR) and effective arterial elasticity) especially in the preload responder group without changes in MAP. This indicates that fluid administration, although it will increase cardiac output, will still reduce arterial load. This condition explains why in some septic patients, despite an increase in cardiac output after fluid administration, there is still no increase in blood pressure. Thus, fluid administration alone is not sufficient to correct hypotension and administration of a vasopressor, such as epinephrine, is reasonable because it may increase SVR. Therefore, administration of fluids without vasopressors during the state of severe hypotension, accompanied by a significant vasodilator component, is futile and does not improve the patient's condition [17,18].

This difference may be due to the administration of a vasopressor such as norepinephrine 0.05 µg/kg/min to all of our study subjects, which led to an increase in SVR and in turn could increase MAP. In a previous study by Garcı´a et al (2015), vasopressor administration was not performed in all subjects because they wanted to see the effect of administering fluid expansion on arterial load [17,18]. Previous experimental studies have suggested that the hemodynamic profile of distributive shock, such as low SVR and high cardiac output (CO) which were frequently seen in septic shock patients, can be induced by fluid administration, resulting in a transformation from a hypodynamic to a hyperdynamic state [19,20]. Responsiveness to fluid is defined as the ability of the heart to significantly increase CO in response to volume expansion. Patients can respond with or without elevated blood pressure. It is not known whether the clinical outcome of fluid administration is better with an increase in arterial blood pressure and volume or with an increase in volume only. Fluid administration alone if aimed at improving both blood flow and blood pressure should be reconsidered because in previous study there was a relatively small increase in MAP in the preload responder group (from 74 to 78 mmHg). Thus, aggressive fluid resuscitation to improve organ perfusion should be considered with caution [17].

In our study, fluid administration of of 10mL/kg and 20mL/kg plus a vasopressor gave the effect of increased MAP, and the difference was statistically significant ($p<0.05$). In the 10mL/kg fluid administration group, in the first 15, 20, and 25 minutes, the MAPs were 94.38; 97.74; and 100.33 mmHg, while in the 20mL/kg group the MAPs were 69.9; 71.7; and 73.22 mmHg respectively. This condition shows that the administration of 10mL/kg fluid provides a higher increase in MAP. As discussed earlier, in previous studies, it was suggested that volume expansion can decrease arterial load, so that although cardiac output and overall blood volume increase and there may be an increase in oxygen perfusion, it is not accompanied by an increase in arterial blood pressure. Volume expansion can trigger a variety of complex processes that affect the arterial, venous and cardiac function systems [21]. Possible mechanisms involved include the blunting of baroreflex-mediated vasoconstriction mechanism in response to hypovolemia, resulting from the administration of intravascular fluid on the responder's preload. Meaning that despite the increased of blood flow, arterial pressure remains minimal due to vasoplegic conditions (such as sepsis) which could reset the cardiovascular system to maintain lower blood pressure than in non-shock conditions. Thus, if flow increases with fluid administration, a decrease in arterial load occurs as a compensatory mechanism to maintain arterial pressure at the same level. In previous studies, a decrease in heart rate after fluid administration also occurred in response to a baroreceptor mechanism that decreased sympathetic activity. Aggressive fluid administration in vasoplegic conditions can also decrease tissue perfusion pressure due to increased central venous pressure (CVP) exceeding MAP [17].

In our study, fluid bolus administration of 30 mL/kg showed significantly different changes in MAP with the 10mL/kg group. The MAP values at 15, 20, and 25 minutes after administration of 30 mL/kg fluid were 65.37; 67.74; and 70.74 mmHg. The group given 30 mL/kg fluid showed an increase in MAP but this value was lower than the 10 mL/kg group and was not significantly different from the 20 mL/kg group. Although fluid supplementation is the first line of management for many cases of circulatory failure, excessive administration in a low resource setting can increase the incidence of respiratory failure, leading to death [7]. In non-responder preload it will actually decrease oxygen distribution due to low hemoglobin associated with hemodilution [18]. Therefore, special care should be taken when administering fluids. It is also necessary to carefully consider the risks and benefits of fluid administration. It should be remembered that the goal of giving fluids at the start of resuscitation is to increase stroke volume and cardiac output. So it is important to evaluate the response.

From our study there were significant differences between the overall treatment and MAP values at 15, 20, and 25 minutes after treatment. A previous study aiming to evaluate the response to fluid challenge in septic patients admitted to the ICU, it was found that 53% had an increase in stroke volume at 10 minutes after fluid administration and 51% continued to have an increase in stroke volume up to 30 minutes after fluid administration, and 41, 3% had a transient response, in which there was no longer an increase in stroke volume at 30 minutes after fluid administration. This indicates that the responsiveness to fluids can be time dependent. Therefore, it is necessary to evaluate the response to fluids at the end of the fluid bolus and 30 minutes post administration to identify the efficacy of fluid infusion in organ dysfunction [22]. Significantly different MAP values after administration of 10 mL/kg, 20 mL/kg, or 30 mL/kg fluids, where administration of 10 mL/kg fluids gave higher MAP values than other groups, could be a consideration for fluid selection in order to prevent fluid overload. A previous study by Marik et al ,which examine optimal fluid resuscitation strategies in patients with severe sepsis and septic shock admitted to the ICU in the United States, found that the mean amount of fluid administered was lower than recommended by the 2016 SSC guidelines [5]. Fluid administration of more than 5 L on the first day of ICU admission is associated with a significantly increased risk of death and resulted in higher hospitalization costs [23]. In another study examining the consequences of fluid restriction in patients with septic shock, it was found that restriction of fluid resuscitation did not result in a decrease in circulating efficacy during the first 24 hours compared with the standard protocol [24].

In addition, although we found that there were significant differences between the 15, 20, and 25 min MAP values with the administration of 10, 20, and 30 mL/kg fluids, it should be remembered that vasopressor administration is important because it can increase MAP more than fluids alone. The combination of the two will have a good effect on increasing cardiac output and improving hypotension. The combination of the two can prevent fluid overload when accompanied by administration of appropriate amounts of fluids and close monitoring. Administration of 10 mL/kg fluid bolus combined with norepinephrine gave a good effect of increasing MAP and was significantly different from the other groups. Administration of these moderate amounts of fluids when combined with vasopressors also results in less hemodilution. Thereby increasing oxygen perfusion to tissues and improving patient outcome [18].

CONCLUSION

There is a significant comparison in the ratio of norepinephrine pre-loading fluid toward MAP in sepsis patients. Comparison of the mean MAP value at 15, 20, 25 minutes was the highest in the 10 mL/KgBW group. Meanwhile, the lowest MAP was found in 30mL/KgBW the group.

CONSENT FOR PUBLICATION

The Authors agree to publication in Journal of Society Medicine.

FUNDING

None.

COMPETING INTERESTS

None.

AUTHORS' CONTRIBUTIONS

All authors significantly contribute to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. Contribute to drafting, revising, or critically reviewing the article. Approved the final version to be published, agreed on the journal to be submitted, and agreed to be accountable for all aspects of the work.

ACKNOWLEDGMENTS

We would like to thank Haji Adam Malik Hospital Indonesia.

REFERENCE

1. Mutsaqof N, Wiharto AA, Suryani E. Sistem Pakar Untuk Mendiagnosis Penyakit Infeksi Menggunakan Forward Chaining. Teknologi & Informasi ITS Smart 2016;10(1969):43.
2. Purwanto DS, Astrawinata DAW. Mekanisme Kompleks Sepsis dan Syok Septik. Jurnal Biomedik (Jbm) 2018;10(3):143.
3. Mahapatra S, Heffner AC. Septic Shock. NCBI Bookshel 2022. Available at: https://www.ncbi.nlm.nih.gov/books/NBK430939
4. Kemenkes RI. Pedoman Nasional Pelayanan Kedokteran Tata Laksana Sepsis. Kemenkes. 2017;(1):43.
5. Rhodes A *et al.* Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016, Intensive Care Medicine. Springer Berlin Heidelberg. 2017.
6. The PRISM Investigators. Early, Goal-Directed Therapy for Septic Shock — A Patient-Level Meta-Analysis. New England Journal of Medicine 2017;376(23):2223–2234.
7. Brown RM, Semler MW. Fluid Management in Sepsis. Journal of Intensive Care Medicine 2019;34(5):364–373.
8. Jozwiak M *et al.* Fluid resuscitation during early sepsis: A need for individualization. Minerva Anestesiologica 2018;84(8):987–992.
9. Evans L. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021, Critical Care Medicine 2021.
10. Santhanam I. A prospective randomized controlled study of two fluid regimens in the initial management of septic shock in the emergency department 2014;24(2008):24–26.
11. Kotfis K. A worldwide perspective of sepsis epidemiology and survival according to age: Observational data from the ICON audit. Journal of Critical Care 2019;51:122–132.
12. Strait JB, Lakatta EG. Aging-Associated Cardiovascular Changes and Their Relationship to Heart Failure. Heart Failure Clinics 2012;8(1):143–164.
13. Nasa P, Juneja D, Singh O. Severe sepsis and septic shock in the elderly: An overview. World Journal of Critical Care Medicine 2012;1(1):23.
14. Ko SY. The association between intravenous fluid resuscitation and mortality in older emergency department patients with suspected infection. International Journal of Emergency Medicine 2019;12:1-8
15. Nasir N. Mortality in sepsis and its relationship with gender. Pakistan Journal of Medical Sciences 2015;31(5):1201–1206.
16. Donnino MW. Randomized, Double-Blind, Placebo-Controlled Trial of Thiamine as a Metabolic Resuscitator in Septic Shock: A Pilot Study. Critical Care Medicine 2016;44(2):360–367.

17. Garcı´a MIM. Effects of fluid administration on arterial load in septic shock patients. Intensive Care Medicine 2015;41(7):1247–1255.
18. Hamzaoui O. Combining fluids and vasopressors: A magic potion?. Journal of Intensive Medicine 2022;2(1):3–7.
19. Cholley BP. Alterations in systemic arterial mechanical properties during septic shock: Role of fluid resuscitation. American Journal of Physiology - Heart and Circulatory Physiology 1995;269(1):38-1.
20. Ricard-Hibon A. Systemic pressure-flow reactivity to norepinephrine in rabbits: Impact of endotoxin and fluid loading. Intensive Care Medicine 1998;24(9):959–966.
21. Biais M. Fluid Responsiveness in the Operating Room. Anesthesiology 2017;September:450–6.
22. Roger C. Time course of fluid responsiveness in sepsis: The fluid challenge revisiting (FCREV) study. Critical Care 2019;23(1):1–10.
23. Marik PE. Fluid administration in severe sepsis and septic shock, patterns and outcomes: an analysis of a large national database. Intensive Care Medicine 2017;43(5):625–632.
24. Hjortrup PB. Effects of fluid restriction on measures of circulatory efficacy in adults with septic shock. Acta Anaesthesiologica Scandinavica 2017;61(4):390–398.

How to cite	Rendi Sidiq, Bastian Lubis, Yutu Solihat. Comparison of Pre-Loading Fluid With Norepinephrine Toward Mean Arterial Pressure (MAP) In Sepsis Patients In Intensive Care Unit (ICU) of Haji Adam Malik General Hospital, Medan. *Journal of Society Medicine*. 2022;1(1): 36-43. DOI Link (https://doi.org/10.25217/ji.vxix.xx)