



Effectiveness of Norepinephrine-Vasopressin Combination in Reducing Mortality in Septic Shock Patients: A Scoping Review

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Abstract Sepsis and septic shock are the major health problems worldwide, including in Indonesia. Sepsis and septic shock are medical emergencies that require adequate prompt resuscitation to reverse tissue hypo-perfusion, which will prevent patient mortality. The latest international guideline on septic shock treatment recommended norepinephrine as a first-line vasopressor followed by dopamine and dobutamine as an alternative vasopressor. However, the practices still vary. Therefore, a scoping review is required to scope the existing article, summarize scientific evidence, and give a bearing on future research regarding the effectiveness of norepinephrine-vasopressin combination in reducing mortality in septic shock patients. This scoping review was covered articles published after 2011. A total of 953 articles were collected. Seven articles comprised of 5 systematic reviews, 1 randomized controlled trial, and 1 cohort study with a total 21,670 of patients, were included for qualitative synthesis. From the analysis, there had not been enough scientific evidence to conclusively determine the combination of vasopressors as the best therapeutic outcome of sepsis treatment. In conclusion, based on the existing articles there is inadequate scientific evidence to definitively conclude the effectiveness of the combination of vasopressors and norepinephrine for the treatment of septic shock patients. Further research is needed to explore the effectiveness of the norepinephrine-vasopressin combination in reducing mortality in septic shock patients.

Keywords: norepinephrine; septic shock; vasopressin

1. Introduction

Sepsis is a life-threatening state of organ dysfunction due to infection that causes dysregulation of the immune response (Cheng *et al.*, 2019; Seymour *et al.*, 2016; Sinto *et al.*, 2018). Meanwhile, a septic shock is a state of sepsis with the addition of circulatory and metabolic abnormalities that required to start of vasopressors immediately to maintain a mean arterial pressure (MAP) 65 mm Hg or greater, and a serum lactate level greater than 2,0 mmol/L following adequate fluid resuscitation (Shankar-Hari *et al.*, 2016). Delayed detection and treatment of sepsis can lead to death (Sinto *et al.*, 2018).

Sepsis and septic shock has been major health problem worldwide (Fleischmann *et al.*, 2016). Although the global epidemiological burden of sepsis is difficult to determine, the recent global data of the incidents of sepsis in seven high-income countries showed that 19,4 million

people suffer from sepsis annually, 5.3 million of those people end with death (Fleischmann *et al.*, 2016; Rudd *et al.*, 2020). A study also estimated that most people with sepsis are citizens of middle to lower-income countries, including Indonesia (Fleischmann *et al.*, 2016).

Sepsis and septic shocks are medical emergencies condition that requires early recognition and adequate prompt resuscitation to reverse tissue hypo-perfusion, which will prevent patient mortality (Dugar *et al.*, 2020; Rhodes *et al.*, 2017). Besides resuscitation with crystalloid, tissue hypo-perfusion can also be reversed by administering vasopressors that could increase blood pressure by inducing vasoconstriction, which will improve tissue perfusion (Ospina-Tascón *et al.*, 2020; Rhodes *et al.*, 2017). The latest international guideline on sepsis treatment recommended norepinephrine as a first-line vasopressor and the addition of vasopressin or epinephrine are recommended to achieve the targeted MAP (Rhodes *et al.*, 2017). Dopamine and dobutamine were recommended as alternative vasopressors where dopamine can be used in bradycardic patients or patients with a lower risk of tachyarrhythmia, while dobutamine is used in patients suffering from persistent hypo-perfusion, despite receiving vasopressors (Rhodes *et al.*, 2017; Russel, 2019). However the use of dopamine and dobutamine instead of norepinephrine still have a weak recommendation due to the low quality of evidence and more trials are needed to accurately confirm these recommendations (Cheng *et al.*, 2019; Rhodes *et al.*, 2017).

This scoping review was conducted to investigate evidence on the effectiveness of norepinephrine-vasopressin combination for the treatment of septic shock patients. More specifically, this scoping review will scope the existing article, summarize scientific evidence, and give a bearing on future research regarding the effectiveness of norepinephrine-vasopressin combination in reducing mortality in septic shock patients.

2. Material and Methods

2.1. Eligibility criteria

This review used a scoping review design. The included articles must be published after the year 2011, from any country in the world, written in English, and investigated the use of norepinephrine, vasopressin, and/or epinephrine in adult septic shock patients (above 18 years old).

2.2. Information sources and study selection process

Articles were searched from several databases. The databases included were PubMed PMC, Science Direct, and ProQuest. Boolean logic utilised as follows, ((Septic Shock OR Endotoxic Shock OR Toxic Shock OR Toxic Shock Syndrome) AND (Norepinephrine OR Arterenol OR Levarterenol OR Levonor OR Levonorepinephrine OR Levophed OR Noradrenaline) AND ((Epinephrine OR 4-(1-Hydroxy-2-(methylamino)ethyl)-1,2-benzediol

OR Adrenaline OR Epifrin OR Epitrate OR Lyophrin OR Medihaler-Epi) OR (Vasopressin OR Antidiuretic Hormones OR Pitressin OR Vasopressin (USP) OR beta-hypophamine) AND (RCT OR Randomized Controlled Trial))). The publication date of the articles was between 2011 to 2020.

3. Results and Discussion

We conducted articles search in PubMed PMC, Science Direct, and ProQuest (Figure 1). Several articles were also found from hand searching in the Journal of Critical Care Medicine. There were 803 articles from PubMed PMC, 153 articles from Science Direct, and 10 articles from ProQuest. From the 966 articles obtained, there were 14 duplicates, resulting in a total of 953 included articles.

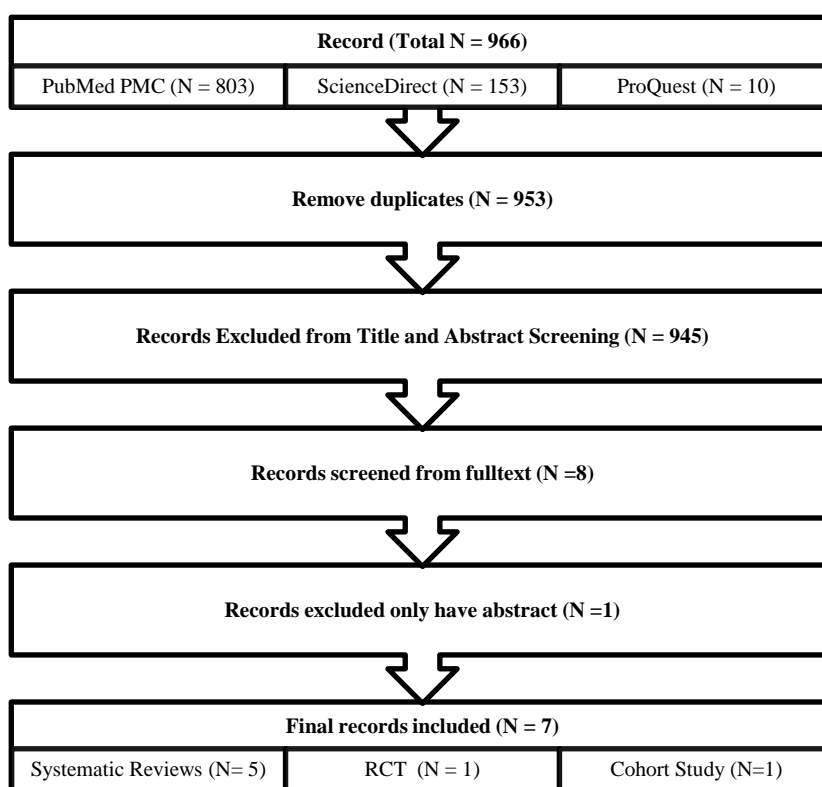


Figure 1. Flow chart for the study selection that search in PubMed PMC, Science Direct, and ProQuest (Page *et al.*, 2021).

After abstract screened in the further step, there were 684 excluded articles as they were unrelated to adult septic shock, 217 unrelated to norepinephrine, 13 unrelated to vasopressin and epinephrine, and 31 unrelated to norepinephrine-vasopressin or norepinephrine-epinephrine combination. Therefore, eight articles went through full-text reading. Afterwards, 1 journal was excluded as it only had an abstract. Finally, there were seven articles included for qualitative synthesis.

The included articles comprise five systematic reviews, one randomized controlled trial, and one cohort study. A total of 21,411 patients were included in the five systematic reviews, 60 from the randomized controlled trial, and 199 from the cohort study. In total, 21,670 patients

were included in the qualitative synthesis of this scoping review. A qualitative synthesis of the seven articles that met the inclusion criteria were summarized in Table 1.

Table 1. Summary of included articles that search in PubMed PMC, Science Direct, and ProQuest.

Author	Study Design	Number of Patients	Research Results
(Mahmoud & Ammar, 2012)	Randomized Controlled Trial	60	The addition of epinephrine to norepinephrine showed positive results for cardiovascular parameters, but negative results for serum lactate and systemic pH when compared to the addition of dobutamine to norepinephrine.
(Ammar <i>et al.</i> , 2019)	Cohort	199	The administration of epinephrine when patients are receiving norepinephrine at a dose of 37-133 µg/min is associated with better hemodynamic stability.
(McIntyre <i>et al.</i> , 2018)	Systematic Review	3,008	The addition of vasopressin to catecholamine vasopressors is associated with a lower risk of atrial fibrillation when compared to catecholamine vasopressors.
(Chen <i>et al.</i> , 2019)	Systematic Review	5,928	The combination of norepinephrine-epinephrine showed better 28-day mortality when compared to the combination of norepinephrine-vasopressin.
(Cheng <i>et al.</i> , 2019)	Systematic Review	5,767	Although the study contains the combinations of norepinephrine-epinephrine and norepinephrine-vasopressin but did not compare the two combinations on the same parameters.
(Oba & Lone, 2014)	Systematic Review	2,811	The combination of norepinephrine and low dose vasopressin is associated with significantly lower mortality when compared with dopamine. It is not so with the combination of norepinephrine-epinephrine.
(Zhou <i>et al.</i> , 2015)	Systematic Review	3,819	The combination of norepinephrine-vasopressin showed a lower probability for mortality compared to the combination of norepinephrine-terlipressin (a synthetic analogue of vasopressin).

From the 7 articles that met the inclusion criteria, 3 articles did not directly compare the norepinephrine-epinephrine and norepinephrine-vasopressin combinations. One randomized controlled trial compared the combinations norepinephrine-epinephrine and norepinephrine-dobutamine where positive effects on hemodynamics and negative effects on serum lactate and systemic pH were found in combinations with epinephrine compared with the addition of dobutamine. Despite showing that the norepinephrine-epinephrine resulted in a better outcome, it did not compare it with the combination of norepinephrine-vasopressin (Mahmoud & Ammar, 2012). The same limitation was found in the cohort study, where they studied the norepinephrine-epinephrine combination but did not compare it with the norepinephrine-

vasopressin combination. Therefore, despite the administration of epinephrine at a certain dose with the combination of norepinephrine resulted in hemodynamic stability, it did not answer the research question (Ammar *et al.*, 2019). The timing of norepinephrine initiation needs to be considered in septic shock patients as an important key role to life support according to the 28-day mortality rate in early NE administration (within two hours) was 29,1% and in late NE administration (after two hours) was 43.3% (Bai *et al.*, 2014). A randomized clinical trial showed a significant association between 6 hours of improvement in septic shock patients after early norepinephrine administration (Permpikul *et al.*, 2019).

A systematic review compared several combinations of vasopressors, including norepinephrine-epinephrine and norepinephrine-dobutamine. However, those two combinations were not compared on the same parameters and did not answer the research question as it did not compare the combinations norepinephrine-epinephrine and norepinephrine-vasopressin (Cheng *et al.*, 2019).

Four systematic reviews showed the comparison of the combinations of norepinephrine-epinephrine and norepinephrine-vasopressin in septic shock patients. However, it was difficult to definitively determine the better combination as those 4 systematic reviews evenly split between the two combinations. The systematic review done by McIntyre *et al.*, (2018) showed that the addition of vasopressin to catecholamine vasopressors was associated with a lower risk of atrial fibrillation compared to catecholamine vasopressors given alone. This study showed that the addition of vasopressin to norepinephrine reduced the incidence of atrial fibrillation, compared to the norepinephrine-epinephrine combination as both are catecholamine vasopressors. Vasopressin could spare adrenergic stimulation by catecholaminergic vasopressors and lower the rate also shorter the duration of atrial fibrillation and should be given only in patients with a high level of cardiac output (McIntyre *et al.*, 2018; Vincent & De Backer, 2013). The systematic review conducted by Oba & Lone, (2014) also showed that compared to dopamine, the combination of norepinephrine-vasopressin showed lower mortality than the combination of norepinephrine-epinephrine. Low-dose vasopressin can significantly reduce mortality compared with dopamine as the vasopressin could prevent myocardial dysfunction and cardiomyopathy by decreasing heart rate without lowering cardiac output (Oba & Lone, 2014; Pollard *et al.*, 2015). Both of these systematic reviews showed that the combination of norepinephrine-vasopressin resulted in a better therapeutic outcome for septic shock patients (McIntyre *et al.*, 2018; Oba & Lone, 2014). However, the other two systematic reviews showed otherwise.

The systematic review done by Chen *et al.*, (2019) showed that the combination of norepinephrine-epinephrine resulted in lower mortality (14,8%) when compared to the

combination of norepinephrine-vasopressin (2,4%). This study also found in refractory to other vasopressors patients, low-dose vasopressin can effectively raise blood pressure and may have other potential physiologic benefits. The synergistic effect of the combination agents could decrease the dosage and adverse effects and was accounted for the top three therapeutic regimens (Chen *et al.*, 2019; Russel, 2019). Moreover, the systematic review done by Zhou *et al.*, (2015) showed similar results, with norepinephrine-epinephrine associated with lower mortality when compared to norepinephrine combined with terlipressin, which is a synthetic analogue of vasopressin. Another study showed no significant difference in mortality between the norepinephrine-vasopressin group compared with the norepinephrine group which combination therapy is only used in resistant septic shock patients (Raza *et al.*, 2020).

This scoping review showed that there had not been adequate scientific evidence to conclusively determine the combination of vasopressors that would lead to the best therapeutic outcome. Despite the results being inconclusive, the review has given a scope of the existing article, summarized scientific evidence, and gave a bearing on future research regarding the effectiveness of norepinephrine-vasopressin combination in reducing mortality in septic shock patients. However, there are limitations in this review: (1) the small number of articles that included and a heterogeneous study method; (2) the results of this review depends on the quality of available studies; (3) only English written studies were included.

4. Conclusion

In conclusion, based on the existing articles there is inadequate scientific evidence to definitively conclude the effectiveness of the combination of vasopressors and norepinephrine for the treatment of septic shock patients. Further research is needed to explore the effectiveness of the norepinephrine-vasopressin combination in reducing mortality in septic shock patients.

Acknowledgement

Not applicable

Conflict of Interest

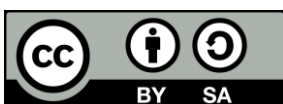
All authors declared that there was no conflict of interest.

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