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ORIGINAL RESEARCH

Comparison Between Norepinephrine-Epinephrine and Norepinephrine-Vasopressin Effectiveness in Reducing Mortality in Septic Shock: A Systematic Review

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ABSTRACT

Background: Sepsis is a state of organ dysfunction caused by the immune system's abnormal response to an infection. Septic shock is sepsis complicated by circulatory and metabolic abnormalities, oftentimes resulting in death. Prompt identification and treatment of septic shock is crucial for the survival of patients. The latest international guideline recommends the administration of norepinephrine as the first line vasopressor, with the addition of epinephrine or vasopressin as an aid in achieving the target MAP (Mean Arterial Pressure).

Methods: This study is a systematic review of literatures from the databases Pubmed PMC, Science Direct, and Proquest. Systematic reviews on septic shock, norepinephrine, and epinephrine or vasopressin were among the inclusion criterias. This resulted in a total of five systematic reviews to be included in the qualitative synthesis.

Results: The five included studies were not in sync as to which vasopressor is best used for the treatment of septic shock patients. One of which did not compare the two combinations within the same category, two of which favored the use of norepinephrine-epinephrine, and the other two favored the use of norepinephrine-vasopressin for the treatment of septic shock patients.

Conclusion: The existing evidence were insufficient to give a conclusion of the best combination of vasopressors for septic shock patients. More research, specifically randomized controlled trials, needs to be conducted on this topic with well defined administration of combinations of vasopressors as an advancement of this systematic review. The writers also recommend the delay of anymore systematic reviews until the former recommendation has been met.

Keywords: Epinephrine; Mortality; Norepinephrine Septic shock; Vasopressin.

INTRODUCTION

Sepsis is a life-threatening condition caused by dysregulation of the immune system in response to an infection, eventually leading to organ dysfunction and death[1]. Annually, there are 30 million cases of sepsis globally, of which 6 million resulted in death. Of all those cases, it is estimated that majority of the patients come from an economically developing country[2,3].

During the year 2014 in America, there are approximately 1,7 million adults that suffer from sepsis and 270 thousand died because of it[4]. According to research done in 16 Asian countries in 2009, the mortality rate of hospital treated septic patients was as high as 44,5%[5]. In Indonesia, the national data on the number of sepsis cases and mortality was not well documented. However, data from Dr. Cipto Mangunkusumo National Central General Hospital in Jakarta shows that out of 84 ICU patients during one month in 2012, 23 of those patients suffered from sepsis with a mortality rate of 47,8% after treatment and 34,7% for early sepsis. Data from Dr. Moewardi Regional General Hospital shows that there were 1909 septic patients from 2016 to 2019[6].

Septic shock is a medical emergency requiring immediate intervention to reduce the risk of patient mortality, of which hemodynamic resuscitation is one of the most crucial in the initial stage. The use of vasopressors aims to reach the target mean arterial pressure (MAP) to ensure adequate organ perfusion. According to the latest guideline in surviving sepsis campaign 2021, the use of norepinephrine as the first line vasopressor is recommended, with the addition of epinephrine or vasopressin as an adjuvant vasopressor[7,8]. This is also supported by a study showing reduced side effects when multi regimen vasopressors are used[9]. Therefore, a systematic review is needed to explore the current literatures available on the comparison of norepinephrine-epinephrine compared to norepinephrine-vasopressin in reducing mortality in septic shock patients.

METHODS

This review was reported using the “Preferred Reporting Items for Systematic Reviews and Meta-Analysis” guideline and written using the “Synthesis without Meta-Analysis” method. This review was designed to answer the question of which combinations of norepinephrine-

epinephrine (NE-EP) or norepinephrine-vasopressin (NE-VP) is more effective in reducing mortality in septic shock patients. This question includes the component of population (septic shock patients), intervention (NE-EP), control (NE-VP), and outcome (mortality).

The included studies for this review had to fulfill several criteria elaborated in the proceeding part. A systematic review, written in English, discussed the use of norepinephrine or epinephrine or vasopressin in septic shock patients. The studies were excluded if it did not meet the inclusion criteria. In addition, duplicates, case reports, interventional and observational studies were excluded.

The systematic reviews included in this systematic review were collected from three online databases, namely ProQuest, Science Direct and PubMed published between 2012 to 2022. The keywords used for this systematic review were “septic shock”, “norepinephrine”, “epinephrine”,“vasopressin”,“mortality” ,and “systematic review”. These keywords were used with medical subject heading (MeSH) terms and formatted with Boolean strategy.

Three authors independently screened the collected articles. Any disagreement was resolved by discussion. Data extraction was done in the same manner, with the extraction of authors’ names, type of study, types of studies included in the systematic review, year of publication, number of patients and research results. The critical appraisal was done using AMSTAR-2 scoring.

RESULT

We conducted articles search in ProQuest, Science Direct and Pubmed PMC. There are 715 articles from Proquest and 234 from Science Direct and Pubmed PMC. Of the 949 articles obtained, there were twenty duplicates, resulting in a total of 929 articles to be screened.

After abstract screening, 790 articles were excluded as they were unrelated to septic shock, sixty eight are unrelated to epinephrine or norepinephrine or vasopressin, five are not human studies, and fifty nine are not systematic reviews. Hence, seven systematic reviews remained for full-text reading. Afterwards, two systematic reviews were excluded as it was unrelated to NE-EP or NE-VP. Finally, there are five systematic reviews included for qualitative synthesis.

There are 21,411 patients included in the studies found in the five systematic reviews. A qualitative synthesis of the reviews are summarized.

DISCUSSION

The results drawn from five systematic reviews included in this review are contradictory to each other. One systematic review does not answer the research question, as the two combinations of vasopressors were not compared within the same parameter[10].

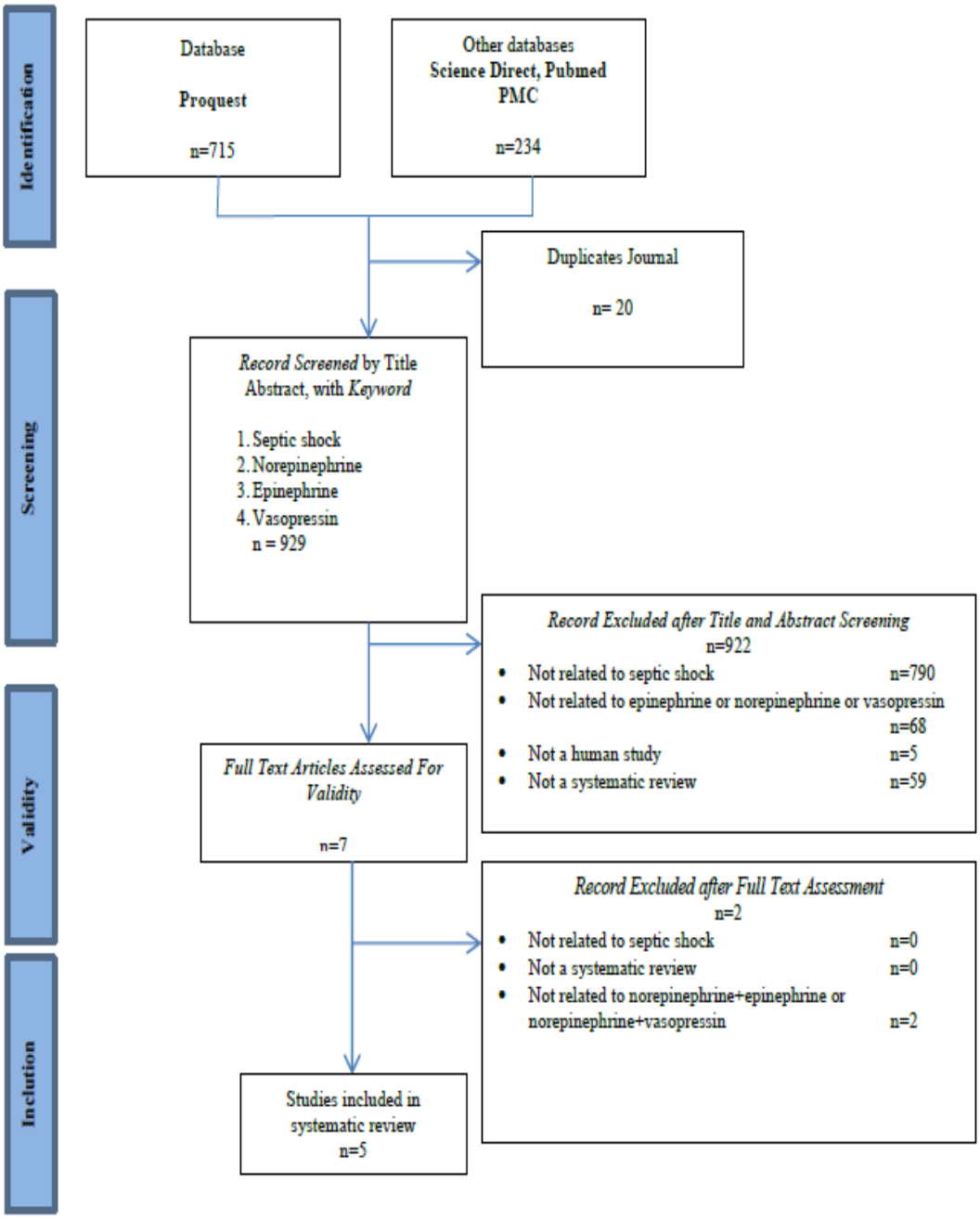

Figure 1. Flow diagram of the research prosedure[10]

Table 1. Summary and AMSTAR-2 Score of Included Studies

Writer	Type of Study	Studies Included	Year	Intervention	Total Patient	Mortality	Risk of Bias for Atrial Fibrillation	Efectivity in Reducing Mortality	AMSTAR-2 Score
Cheng et al	Meta-analysis	RCT	2019	Norepinephrine + dobutamine	5,767			85.9%	13.3
				Norepinephrine + epinephrine				74.6%	
Chen et al	Meta-analysis	RCT	2019	Epinephrine vs norepinephrine + dobutamine	161 vs 169	39.7% vs 34.3%			3.7
				Vasopressin+norepinephrine vs norepinephrine	41 vs 41	46.3% vs 44%			
				Epinephrine vs norepinephrine + dobutamine	15 vs 15	60% vs 53.3%			
				Vasopressin+norepinephrine vs norepinephrine	10 vs 8	80% vs 87.5%			
				Norepinephrine + dobutamine vs norepinephrine + epinephrine	30 vs 30	50% vs 53.3%			
				Epinephrine vs norepinephrine + dobutamine	10 vs 11	40% vs 45.4%			
				Epinephrine vs dopexamine + norepinephrine	10 vs 12	30% vs 16.7%			
Zhou et al	Meta-analysis	RCT	2015	Vasopressor combination (Norepinephrine, dopamine, vasopressin, epinephrine, terlipressin, phenylephrine)	3,819	1,915			9.2
McIntyre et al	Systematic Review and Meta-analysis	RCT	2018	Vasopressin + norepinephrine vs norepinephrine	82		High		12.8
				Vasopressin + norepinephrine vs norepinephrine	30		High		
Oba and Lone	Meta-analysis	RCT	2014	Vasopressin + norepinephrine vs norepinephrine	778	61%			5.3
				Vasopressin + norepinephrine vs norepinephrine	23	46%			
				Norepinephrine + dobutamine vs epinephrine	55	50%			
				Norepinephrine + dobutamine vs epinephrine	68	68%			
				Norepinephrine + dobutamine vs epinephrine	63	46%			
				Norepinephrine vs dopamine vs norepinephrine	58	40%			
				Norepinephrine vs dopamine vs epinephrine	66	55%			

Two combination systematic reviews favor the of NE-EP, whereas the other two favor the combination of NE-VP[11–14].

The included reviews showed no methodological heterogeneity, with all of them only including randomized controlled trials into their qualitative synthesis. Risk of bias was minimized by the reviews' adherence to the PRISMA protocols, with the protocol of the study by Cheng et al and McIntyre et al already published in PROSPERO.

The systematic review by Cheng et al. compares several combinations of vasopressors, including NE-EP and NE-VP. The former combination ranks third highest in 28-day mortality, first in myocardial infarction and peripheral ischemia. On the other hand, NE-VP ranks fourth in ICU mortality. Despite the inclusion of the two relevant combinations, they were never compared within the same parameter, hence a valid comparison cannot be made[10].

Conclusions from the other four systematic reviews cannot be drawn, as the results contradict each other. The systematic review by McIntyre et al. showed that the addition of vasopressin to catecholamine vasopressors is associated with a lower risk for atrial fibrillation and stable hemodynamic status[13]. Likewise, the systematic review by Oba and Lone shows that the combination of NE-VP results in a lower mortality rate compared to NE-EP with norepinephrine as the control[14].

On the contrary, the systematic review by Chen et al. shows that the combination of NE-EP causes a lower mortality rate compared to NE-VP[12]. The systematic review by Zhou et al shows that NE-EP is associated with a lower mortality rate, compared to norepinephrine-terlipressin which is a synthetic analogue of vasopressin[11].

Asides from the above reasons, the authors' difficulty in deriving a conclusion is due to even more contradictive results from literatures about this topic, especially those studying vasopressin. The randomized controlled trial included in VAAST (Vasopressin and Septic Shock Trial) shows that the administrations of NE-VP significantly reduced twenty eight and ninety days mortality[15]. This is in line with the systematic reviews done by McIntyre et al. and Oba and Lone. In contrary, several studies have shown that the administration of vasopressin significantly increased 24-hour serum lactate, which is an indicator of mortality in septic shock patients.

The systematic review by Cheng et al. describes the SUCRA (Surface Under the Cumulative Ranking Curve) values of some combinations of vasopressors, including norepinephrine-epinephrine and norepinephrine-vasopressin across different parameters. The two parameters directly linked to mortality are 28-days mortality and ICU mortality rate. NE-EP has a 74.6% SUCRA value in reducing 28-days mortality rate. It also mentioned that NE-VP has a SUCRA value of 62.8% in reducing ICU mortality rate[10].

Table 2. Summary of Results of Included Studies

Writer	Year	Research Results
Cheng et al	2019	Although the study contains the combinations of norepinephrine-epinephrine and norepinephrine-vasopressin but did not compare the two combinations on the same parameters.
Chen et al	2019	The combination of norepinephrine-epinephrine showed better 28-day mortality when compared to the combination of norepinephrine-vasopressin.
Zhou et al	2015	The combination of norepinephrine-vasopressin showed a lower probability for mortality compared to the combination of norepinephrine-terlipressin (a synthetic analogue of vasopressin).
McIntyre et al	2018	The addition of vasopressin to catecholamine vasopressors is associated with a lower risk of atrial fibrillation when compared to catecholamine vasopressors.
Oba and Lone	2014	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.

No conclusion can be made from this systematic review of systematic reviews as the results were contradictory to each other. The authors maintain that research on vasopressor combinations are of vital importance, from which its reasoning is based on guideline recommendations and research showing reduced side effects when multiple vasopressors are used instead of a single therapy[7,9]. Therefore, the authors suggest for more research to be conducted on the comparison of NE-EP and NE-VP as treatment options to reduce the mortality in septic shock patients. The authors also suggest a more detailed documentation of the combinations of vasopressors used and its dosages. In addition to that, the

patient data (especially comorbidity) and timing of vasopressor administration is also to be documented in more detail. These statements are supported by research showing that patients with more than four comorbidities have a higher mortality rate and timing of vasopressor administration majorly affects patient outcome.

CONCLUSION

Based on the existing articles there is inadequate scientific evidence to reach a conclusion. Further research is needed to provide more scientific evidence on the effectiveness of the norepinephrine-vasopressine combination in reducing mortality in septic shock patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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