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NORADRENALINE OR DOPAMINE IN SEPTIC SHOCK - A LITERATURE REVIEW

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ABSTRACT

Introduction and purpose: Septic shock is a common cause of death that is hard to treat and choosing the most effective medication remains a major clinical challenge. The aim of this study is to provide key information about this clinical condition and to compare the drugs most frequently used in the treatment process: noradrenaline and dopamine.

Materials and methods: A literature search was conducted using the medical database PubMed and Google Scholar. Articles were retrieved using the keywords: „Noradrenaline” „Dopamine” „Sepsis” „Septic shock” „Hipotension” in appropriate configuration.

Results: 8 studies were found with relevant topics. For of these studies were excluded due to lack of information in the articles or discrepancies in their topics. Finally, 4 meta-analyses were systematically analyzed in our work.

Conclusions: According to the available medical literature, recommendations and guidelines, the use of Noradrenaline in patients with septic shock is usually the most appropriate choice. However, the choice of Dopamine is also available, especially in patients with bradycardia, but its use can be linked with a higher risk of cardiac complications.

KEYWORDS

Noradrenaline, Dopamine, Sepsis, Septic Shock, Hypotension

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1. Introduction

Septic shock is the most severe form of sepsis and one of the leading causes of death in Intensive Care Units all around the world [1]. Septic shock defined in Sepsis-3 is a condition caused by infection, leading to severe organ dysfunction. The most severe and life threatening dysfunction being hypotension requiring vasopressor and elevated >2 mmol/l lactate despite good hydration. [2] Despite development in diagnostics and treatment the mortality of septic shock is still surpassing 40% [3]

1.1. Sepsis

Sepsis is a life-threatening organ dysfunction caused by an inadequate regulation of the body's response to infection. According to WHO, based on data from the year 2020, more than 48.9 million patients suffered from sepsis, and there have been around 11 million deaths related to sepsis, which is around 20% of the total world deaths in that year. Almost 50% of those deaths were children under 5 years old [4]. Anyone with an infection or injury has the potential to develop sepsis. Certain groups are more prone to developing sepsis, including the elderly, pregnant women, children, and patients who have been previously hospitalized — especially those treated in intensive care units. Sepsis lacks a clear and consistent pattern of symptoms, which makes diagnosis challenging. Sepsis can present with symptoms such as fever, difficulty breathing, chills, muscle pain, tachycardia, reduced urine output, and cognitive impairment. Because these symptoms are common and non-specific, it is often difficult to distinguish sepsis from other, less severe illnesses with lower mortality.

Septic shock is a specific form of sepsis with heavy dysfunctions from the cardiovascular and metabolic systems, which are correlated with increased mortality risk. It is characterised by hypotension requiring vasopressor drugs and a high lactate levels in blood. Septic shock is posing a challenge especially for doctors working in intensive care units. Around 10.4% of patients at the moment of admission to ICU are already in septic shock and 8.3% of patients will develop septic shock in the process of treatment. According to the epidemiological research, 33% of patients in the ICU suffer from sepsis, of which 30-37% are in septic shock. Mortality of septic shock is high, according to a meta-analysis of cases from 2005-2018, 36.7% of people in septic shock will die in the next 30 days. [1] In developing countries, the mortality increases to even 46% [5]

Sepsis and septic shock are conditions associated with very high mortality, not only due to the underlying pathophysiological mechanisms but also because of the challenges in accurately diagnosing these clinical states. Patients with sepsis are often initially misdiagnosed with other conditions, leading to delays in appropriate and effective treatment. To address this issue, specialized diagnostic scales have been developed and are widely used to simplify, accelerate, and guide the diagnostic process from the onset. Additionally, scientific societies have launched public initiatives—such as the *Surviving Sepsis Campaign*—to standardize diagnostic protocols and educate medical personnel on how to respond effectively when sepsis is suspected [6].

1.2. Methods for assessing septic shock**SOFA scale.**

SOFA Scale is a tool used to evaluate the degree of organ failure in patients in severe clinical conditions and to assist in the diagnosis of sepsis. It has been created to objectify the evaluation of organ function in the organism. It is routinely used in the intensive care units to monitor the state of the patients. It is based on assessment of 6 systems critical for survival.

- 1) Circulatory system- Blood pressure and the need for vasopressors
- 2) Respiratory system- index of $\text{PaO}_2/\text{FiO}_2$
- 3) Coagulation system- Platelet count
- 4) Renal parameters - Diuresis and creatinine concentration
- 5) Liver parameters - Bilirubin concentration
- 6) Nervous system - Glasgow Coma Scale (GCS)

All of those systems are rated on a 5-point scale from 0 to 4, where 4 is the most severe form of system failure. The results of each system are then summed up, giving the final result that can range from 0 to 24. An increase of ≥ 2 in comparison to the initial state informs us about increasing organ failure, which indicates that the risk of death increases around 10% [7].

qSOFA scale

Due to the complexity of the SOFA scale, a simplified version called **qSOFA** (quick SOFA) was developed. This quicker assessment enables earlier diagnosis and more timely initiation of treatment. The qSOFA scale includes three components, and a score of **2 or more** suggests a possible sepsis diagnosis. Those 3 components are:

- 1) Systolic pressure < 110 mm Hg
- 2) Respiratory rate > 22 /min
- 3) Altered state of consciousness

In comparison with the SOFA scale, the shortened version can be used already at the time of physical examination of the patient with no need to wait for any lab results, which allows directing further diagnostic and treatment processes. The use of this scale improves the diagnostic process and reduces the likelihood of misdiagnosis, making it a valuable tool in both internal medicine wards and emergency medicine settings. [8]

Sepsis 3 and septic shock.

Sepsis-3 is a set of criteria established in 2016 to unify the definition of sepsis and to distinguish it from septic shock. This revised definition enables better identification of patients requiring further diagnostic evaluation and helps improve treatment outcomes.

The distinction between sepsis and septic shock is clinically important, as septic shock is considered a severe subtype of sepsis. A diagnosis of septic shock requires a SOFA score of **2 or higher**, along with the presence of the following three persistent criteria:

- 1) Persistent hypotension
- 2) Need to use vasopressors (e.g. noradrenaline/dopamine) to maintain MAP (Mean arterial pressure) ≥ 65 mmHg
- 3) Lactate level > 2 mmol/L despite adequate fluid resuscitation.

These criteria allow for an objective diagnosis of septic shock and allow to guide the treatment plan as early as possible. Early identification enables earlier treatment, which can significantly reduce mortality that is as high as 40% in cases of septic shock. [8]

Treatment in septic shock [6]

Septic shock and sepsis, being medical emergency conditions, need to be treated as soon as possible. According to the guidelines, treatment should be started not later than 1 hour from the time of diagnosis [6]. The treatment of septic shock involves several key components aimed at stabilizing the patient and addressing the underlying infection. The main therapeutic approaches include: antibiotic therapy, fluid resuscitation, vasopressor support, oxygen therapy, when necessary, respiratory support, and, control of the infection source.

Antibiotics

Broad-spectrum antibiotics, such as ceftriaxone, should be used as initial treatment. Once the results of the antibiogram are available, the antibiotic should be adjusted accordingly to enable more targeted therapy.

Fluid resuscitation

30ml/kg of crystalloids should be administered in the first 3 hours with the goal to maintain MAP ≥ 65 mmHg.

Vasopressors treatment

Included in the treatment as soon as MAP < 65 mmHg in spite of adequate fluid therapy. Most commonly administered medication being Noradrenaline or Dopamine. In case of inadequate results of the treatment, adding of Vasopressin or Dobutamine should be considered.

Oxygen therapy and respiratory support

The main goal is to maintain oxygen arterial saturation $\geq 92\%$, PaO₂ > 60 mmHg, with the use of oxygen administered through an oxygen mask or, in case of respiratory failure, intubation and mechanical ventilation.

Control of the infection source

Evaluation of possible infection sites and potential surgical intervention, like drainage of abscesses or removal of infected catheters, is advised to be done within the first 12h from the moment of sepsis diagnosis.

Further symptomatic treatment

In case of persisting hypotension, a good addition to treatments are steroids like Dexamethasone. In case of hyperglycemia, insulin therapy is advised with the goal of keeping glycemia in the range 140-180 mg/dl

Appropriate vasopressor therapy is a critical component of septic shock management and can be a determining factor in a patient's survival.

In this paper, we present a literature review and discuss the efficacy of hypotension treatment using Noradrenaline in comparison with Dopamine in the context of reducing the mortality of patients and the potential side effects that can lead to death.

2. Methods

A literature search was conducted using the medical database PubMed, Google Scholar and National library of medicine. Articles were retrieved using the keywords: „Noradrenaline” „Dopamine” „Sepsis” „Septic shock” „Hipotension” in appropriate configurations. Eight papers were found regarding the comparison of efficacy of Dopamine and Noradrenaline treatment in patients with septic shock.

We identified four meta-analyses that collectively included 55 randomized trials and 5 observational studies, analyzing a total of 13,158 patients. However, it should be noted that some of the original studies may have been included in more than one meta-analysis, leading to potential duplications of considered patients.

One of the papers found in the literature search has been excluded based on the language barrier - it has been written in Chinese [9]. Two papers have been excluded from further analysis because they were not completely aligned with the subject of the paper - the authors compared the efficacy of treatments based on combinations of drugs and did not compare the efficacy of single drugs [10][11]. One paper was excluded because of lack full details of the study - only an abstract with a general description of the study was available [12].

3. Results

Table 1. Results of article search

Name of research	Type and quantity of research	amount of patients	Results
De Becker et al. 2012 [13]	5 observational i 6 randomized trials	2768	Higher mortality in patients treated with Dopamine Increased risk of arrhythmias
Ruslan, M.A et al. 2021 [14]	11 randomized trials	4803	Lower risk of Arrhythmias in treatment with Noradrenaline
Vasu et al. 2011 [15]	6 randomized clinical trials	2043	Statistically significant lower risk of arrhythmias in treatment with Noradrenaline in comparison to Dopamine
Avni T.et al. 2015[16]	32 randomized control trials	3544	Lower mortality in treatment with Noradrenaline Lower risk of arrhythmia in treatment with Noradrenaline in comparison to Dopamine

In the paper by De Becker et al. 2012 an analysis was reported consisting of 5 observational and 6 randomized trials with 2768 patients in total. In analysis of the observational trials it has been observed that there is an increased mortality in patients who were treated with Dopamine (relative risk, 1.23; confidence interval, 1.05-1.43; $p < .01$). Similarly, in the randomized trials there has been increased mortality in patients who were treated with Dopamine (relative risk, 1.12; confidence interval, 1.01-1.20; $p = .035$). In two included trials there has been an increase in Arrhythmias in patients treated with Dopamine in comparison to patients treated with Noradrenaline (relative risk, 2.34; confidence interval, 1.46-3.77; $p = .001$)

The paper by Ruslan et al. 2021 reports an analysis of 11 randomized trials in which 4803 patients in total were examined. A decreased risk of arrhythmias in patients treated with Noradrenaline in comparison to patients treated with Dopamine or any other vasopressors was observed (RR 0.64; 95% CI, 0.42 to 0.97; $P = 0.030$; $I^2 = 64\%$). The authors also look at the efficacy of keeping the targeted mean arterial pressure but were unable to determine any difference in the efficacy between Dopamine and Noradrenaline (RR = 1.44 {0.32, 6.54}, $P = 0.64$ $I^2 = 94\%$). Summarising, the authors recommend the use of Noradrenaline due to its lower risk of side effects, despite no significant difference in mortality between the two considered treatments.

Paper by Vasu et al. 2011 reports an analysis of 6 randomized clinical trials in which 2043 patients took part. The authors observed a decrease in mortality of patients treated with Noradrenaline in comparison to patients treated with Dopamine (RR: 0.91 (95% CI 0.83 to 0.99; $P = .028$). A decrease in the occurrence of arrhythmias in patients treated with noradrenaline in comparison to patients treated with dopamine (RR: 0.43 (95% CI 0.26 to 0.69; $P \leq .001$) was observed. The conclusions of the analysis also showed statistically significant superiority in treatment patients with septic shock with Noradrenaline than with Dopamine.

In the paper by Avni et al. 2015 an analysis was carried out of 32 trials in which 3544 patients took part. The authors report lower mortality in patients treated with Noradrenalin in comparison to Dopamine RR 0.89 (95% CI 0.81-0.98). It has also been observed lower risks of arrhythmias in treatment with Noradrenaline rather than any other vasopressors, especially Dopamine. There has been no other mortality benefit demonstrated in the paper, but based on the ones presented, Noradrenaline is the superior choice.

4. Discussion

Sepsis and septic shock present a major clinical challenge, both in diagnosis and treatment. Early diagnosis is a critical factor that significantly influences a patient's survival chances. To simplify diagnostics, dedicated scales were proposed to accelerate treatment in these clinical conditions. One of the most important aspects of treatment is maintaining a mean arterial pressure (MAP) ≥ 65 mmHg. To achieve this level of MAP we use Vasopressors out of which the most commonly used are Noradrenaline and Dopamine. After reviewing the meta-analyses presented above, we found that the use of Noradrenaline is associated with a better safety profile in comparison with the treatment based on Dopamine. The treatment with Dopamine is associated with a greater risk of arrhythmia. In 3 out of 4 papers presenting a comparison of these two treatments, a higher mortality was observed when Dopamine was used as the main treatment. For the sake of a clear comparison, we limited our analysis to the use of two medications in monotherapy, although this approach is not commonly practised in clinical settings [6]. There is also research done to compare the mechanisms of action of those drugs that find some difference between how they achieve their targeted action and which side effects are caused by them [17]. It should be considered that the treatment regimens used in clinical practice for patients with septic shock often make it difficult to interpret outcomes accurately [6]. This is due to the simultaneous use of multiple drugs, potential drug interactions, and unpredictable patient-specific responses based on their clinical condition.

5. Conclusion

Noradrenaline should be recommended as the first-choice drug for patients in septic shock due to its better safety profile and efficacy in comparison to Dopamine. However, in the lack of access to Noradrenaline or in other cases when usage of Noradrenaline is unavailable, usage of Dopamine is also an option, but this drug should be used with extra care, especially considering arrhythmias, which Dopamine has a greater risk of.

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Authors' contributions:

All authors contributed to the article.

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