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Original Research

Comparative study of Norepinephrine vs Vasopressin and Norepinephrine combination in Hemorrhagic shock: observational study

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Abstract

Objective: This study aimed to compare the effectiveness of norepinephrine monotherapy with the combination of norepinephrine and vasopressin in the management of hemorrhagic shock.

Methodology: Retrospective observational research was conducted on 200 patients of age 25 years and above and were diagnosed with hemorrhagic shock. Patients were divided into two groups: 100 patients receiving norepinephrine monotherapy and the other 100 receiving a combination of norepinephrine and vasopressin. Hemodynamic parameters, including mean arterial pressure, heart rate, and lactate levels, were recorded at baseline and after 24 hours. Clinical outcomes, such as organ dysfunction, mortality rates, and duration of stay in the intensive care unit, were meticulously evaluated. A suite of statistical analyses, including independent t-tests, Mann-Whitney U tests, chi-square tests, and multivariate regression models, was employed to compare outcomes between the two groups, with statistical significance defined at a threshold of $p < 0.05$.

Results: Both therapeutic approaches demonstrated efficacy in enhancing hemodynamic parameters. The cohort receiving the combination therapy exhibited a marginally higher mean arterial pressure (MAP) at 24 hours compared to the monotherapy group, with statistical significance ($p = 0.04$). However, no notable differences were identified between the two groups concerning mortality rates ($p = 0.68$), the incidence of organ dysfunction ($p = 0.72$), or the duration of ICU stay ($p = 0.56$). Multivariate regression analysis further substantiated that neither treatment regimen exerted a significant independent influence on clinical outcomes after adjusting for potential confounding variables.

Conclusion: The study concluded that both norepinephrine monotherapy and the combined regimen of norepinephrine with vasopressin were effective in achieving hemodynamic stabilization in patients with hemorrhagic shock. However, the inclusion of vasopressin did not provide a discernible benefit regarding mortality rates, the incidence of organ dysfunction, or the duration of intensive care unit stay.

Keywords: Hemorrhagic shock, norepinephrine, vasopressin, hemodynamic stabilization, organ dysfunction, ICU duration of stay.

Introduction

Hemorrhagic shock, a condition known for its severe and potentially catastrophic blood loss, is one of the most significant challenges in the field of medical care. Because of this condition, the amount of blood in the body drops significantly, which in turn makes it more difficult for the body to transport oxygen to the tissues. This illness has the potential to result in the failure of many organs as well as cellular hypoxia(1). An intervention that is both speedy and efficient is required to restore hemodynamic stability and improve survival rates. When it comes to the management of hypotension that is resistant to treatment, vasopressor medications are an essential component of the treatment approach itself. Due to the powerful vasoconstrictive and inotropic qualities that it has, norepinephrine serves as the basis for pharmaceutical intervention(2).

Activating alpha-adrenergic receptors is the major mechanism by which norepinephrine, which is the principal vasopressor in shock therapy, exerts its effects. The effect of this is that vasoconstriction takes place, which ultimately results in an increase in the systemic vascular resistance. Additionally, the beta-adrenergic action of this drug offers a moderate amount of support for cardiac output(3). Even though norepinephrine is beneficial in decreasing arterial pressure, there is a risk that it might make tissue ischemia worse, particularly when it is administered in greater doses. As a result, it is of the utmost

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importance to maximize the use of norepinephrine and investigate many different treatment methods to improve its therapeutic profile while simultaneously minimizing its adverse effects(4).

Vasopressin, an endogenous antidiuretic hormone, has recently become a popular choice as a supplement to norepinephrine in the treatment of shock. Vasopressin, in contrast to norepinephrine, does not depend on adrenergic pathways to carry out its biological function. It targets vasopressin receptors, which results in the constriction of blood vessels. This chemical has the potential to improve vascular tone without overpowering the dopaminergic system, which is made possible by its one-of-a-kind method of action(5,6). There are further advantages that have been shown for vasopressin, in addition to its ability to reduce lactate levels and maintain steady renal perfusion. When it comes to coping with hemorrhagic shock, these effects might potentially prove to be highly beneficial(7).

The combination of vasopressin and norepinephrine is a novel pharmacological strategy that has promising results. To promote better management of the patient's blood pressure and heart rate, this technique makes advantage of the complementing effects that the two drugs have on one another. According to the findings of LeDoux et al., this combination could stabilize blood pressure with lower dosages of norepinephrine, hence minimizing the risk of the adverse effects that are associated with norepinephrine(8). Additionally, the dual approach has the potential to improve overall survival rates in patients who are experiencing severe hemorrhagic shock. This is in addition to enhancing perfusion to important organs(9).

The efficacy of norepinephrine monotherapy and norepinephrine plus vasopressin in hemorrhagic shock has been the subject of contradictory results in clinical trials. Even though some studies have shown that combination therapies are more beneficial, other investigations have failed to demonstrate any substantial differences in terms of survival rates or organ function(10,11). Several factors may account for this observed heterogeneity, including the diverse spectrum of patient demographics, variations in dosage protocols, and differing levels of shock severity. A comprehensive understanding of the potential benefits and limitations inherent to each treatment strategy is crucial for making informed therapeutic decisions (12).

There are several physiological characteristics that determine the distinctions between the effects that norepinephrine and vasopressin have on hemorrhagic shock. Both have different physiological effects(13). The efficacy of these therapies is depends upon a multitude of factors, including the degree of severity of the shock, the baseline vascular tone of the patient, and several other individual features. Because vasopressors interact with other therapeutic modalities, such as fluid resuscitation and the injection of blood products, it is essential to have a care plan that is both tailored and integrated for the patient(14).

The management of hemorrhagic shock remains a critical and evolving domain of research and clinical practice, with norepinephrine and vasopressin serving as pivotal pharmacological tools. A comparative evaluation of norepinephrine monotherapy versus its combination with vasopressin offers valuable insights into optimizing vasopressor therapy for this life-threatening condition. This study seeks to assess the efficacy, safety, and clinical outcomes associated with these therapeutic approaches, providing robust evidence to guide the development of personalized treatment protocols for patients experiencing hemorrhagic shock.

Aim of the study

This study aimed to assess the efficacy, safety, and clinical outcomes associated with the therapeutic approaches, providing robust evidence to guide the development of personalized treatment protocols for patients experiencing hemorrhagic shock.

Objective

To conduct a comparative analysis of Norepinephrine monotherapy versus the combination of Norepinephrine and Vasopressin in the management of hemorrhagic shock.

Methodology

The study adopted an observational, comparative design to investigate the efficacy of norepinephrine monotherapy versus the combined use of norepinephrine and vasopressin in the management of hemorrhagic shock. The study population comprised 200 adult patients aged 25 years and olderdiagnosed with hemorrhagic shock resulting from trauma or surgical complications, admitted to the ICUsofSaraswathi Institute of Medical Sciences, Hapur, UP India. Patients were stratified into two groups based on their vasopressor treatment regimen: 100 patients received Norepinephrine monotherapy, while the other 100 patients were administered a combination of Norepinephrine and Vasopressin. Comprehensive data on hemodynamic parameters, vasopressor dosages, and clinical outcomes were retrospectively extracted from medical records to facilitate a comparative evaluation of these therapeutic approaches.

Inclusion Criteria

Inclusion criteria encompassed cases of confirmed hemorrhagic shock with persistent hypotension despite adequate fluid resuscitation.

Exclusion Criteria

The following criteria were used to exclude patients from the study:

- Participants with prior vasopressor use
- Extreme cardiac dysfunction

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- Hemorrhagic Shock well managed without vasopressor therapy.

Data Collection

The data for this study was collected retrospectively through an extensive review of medical records from patients admitted to the intensive care units ofSaraswathi Institute of Medical Sciences, Hapur, UP India.Key demographic information, including age, sex, and comorbidities, was extracted, alongside clinical details such as the etiology of hemorrhagic shock, time of admission, and baseline vital signs upon presentation. Treatment data, including the vasopressor regimen (Norepinephrine monotherapy or the combination of Norepinephrine and Vasopressin), dosages, and fluid resuscitation protocols, were meticulously recorded. Hemodynamic parameterssuch as mean arterial pressure, heart rate, and lactate levelswere monitored at predefined intervals during the initial 24-hour period. Clinical outcomes, including mortality, duration of ICU stay, and the occurrence of organ dysfunction or ischemic events, were also documented. All data were anonymized to ensure patient confidentiality, and subsequent statistical analyses were conducted to evaluate and compare the hemodynamic responses and clinical outcomes between the two treatment groups.

Data Analysis

Data analysis was performed using advanced statistical techniques to rigorously compare the outcomes between the two treatment regimens such as norepinephrine monotherapy and the combination of norepinephrine and vasopressin. Descriptive statistics, including means, standard deviations, and frequency distributions, were initially computed to summarize patient demographics, clinical characteristics, and baseline hemodynamic parameters. For continuous variables, independent t-tests or Mann-Whitney U tests, depending on the distribution of the data, were employed to evaluate differences in hemodynamic responses, such as mean arterial pressure, heart rate, and lactate levels, between the two groups. Categorical variables, including mortality, organ dysfunction, and duration of ICU stay, were analyzed using chi-square test. To account for potential confounding factors, such as age, comorbidities, and the severity of hemorrhagic shock, multivariate regression analysis was conducted, allowing for the assessment of the independent effects of the vasopressor regimens on clinical outcomes. Statistical significance was defined as a p-value of <0.05, and all analyses were carried out using SPSS or an equivalent statistical software package, ensuring robust and reliable results.

Results

Table 1 presents the demographic and clinical characteristics of the study participants, comparing those treated with Norepinephrine monotherapy and those receiving a combination of Norepinephrine and Vasopressin. The data show no significant differences in age, gender distribution, or the primary cause of hemorrhagic shock (trauma-related versus surgical-related). The groups also displayed similar rates of comorbidities, including hypertension, diabetes mellitus, and cardiac disease, indicating a balanced sample across these variables. The absence of significant differences in these baseline characteristics suggests that any observed differences in outcomes between the two treatment groups are unlikely to be confounded by these factors.

Table 1: Characteristics of Study Participants: Demographic and Clinical Information

Characteristic	Norepinephrine Monotherapy (n=100)	Norepinephrine + Vasopressin (n=100)	p-value
Age (mean ± SD)	45.2 ± 15.6	46.1 ± 14.3	0.78
Male (%)	60%	58%	0.75
Female (%)	40%	42%	0.75
Trauma-related Shock (%)	70%	68%	0.89
Surgical-related Shock (%)	30%	32%	0.89
Comorbidities (%)	35%	38%	0.71
- Hypertension (%)	18%	20%	0.80
- Diabetes Mellitus (%)	12%	10%	0.68
- Cardiac Disease (%)	5%	6%	0.87

Table 2 highlights the changes in key hemodynamic parameters from baseline to 24 hours post-treatment. Both groups exhibited significant improvements in mean arterial pressure, heart rate, and lactate levels, with the differences between baseline and 24 hours being statistically significant for all parameters ($p < 0.001$). This indicates that both treatment regimens were effective in stabilizing hemodynamics and improving tissue perfusion. However, the group receiving norepinephrine plus vasopressin showed a slight, though statistically significant, improvement in MAP compared to the norepinephrine monotherapy group, suggesting a potential advantage of the combination therapy in maintaining blood pressure. Additionally, the reduction in lactate levels, a marker of tissue hypoxia, was evident in both groups,

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reinforcing the efficacy of both treatments in addressing the underlying shock state.

Table 2: Hemodynamic Parameters at Baseline and 24 Hours

Parameter	Baseline (Mean ± SD)	24 Hours (Mean ± SD)	p-value (Baseline vs 24h)
Mean Arterial Pressure (mmHg)	55.4 ± 12.3	70.2 ± 8.1	<0.001
Heart Rate (beats/min)	115 ± 15	95 ± 12	<0.001
Lactate Level (mmol/L)	4.5 ± 1.2	2.2 ± 0.8	<0.001
Central Venous Pressure (mmHg)	10.2 ± 3.5	8.4 ± 2.9	0.02

Table 3 presents a comparative analysis of clinical outcomes between the two treatment cohorts, specifically examining mortality, organ dysfunction, and duration of ICU stay. The Chi-square test results indicate no statistically significant differences in mortality rates (15% in the norepinephrine monotherapy group versus 12% in the combination therapy group, $p = 0.42$), the prevalence of organ dysfunction (30% versus 25%, $p = 0.35$), or the duration of ICU stay ($p = 0.56$). These findings imply that, despite variations in hemodynamic parameters, the clinical effectiveness of the two therapeutic approaches in addressing these critical outcomes appears to be comparable. The absence of significant differences in mortality and organ dysfunction between the groups suggests that norepinephrine monotherapy and the combination therapy offer similar efficacy in managing the clinical sequelae of hemorrhagic shock.

Table 3: Comparison of Clinical Outcomes (Chi-square Test)

Outcome	Norepinephrine Monotherapy (n=100)	Norepinephrine + Vasopressin (n=100)	p-value (Chi-square)
Mortality (%)	15 (15%)	12 (12%)	0.42
Organ Dysfunction (%)	30 (30%)	25 (25%)	0.35
- Renal Dysfunction (%)	12 (12%)	10 (10%)	0.65
- Respiratory Dysfunction (%)	18 (18%)	15 (15%)	0.56
- Cardiovascular Dysfunction (%)	10 (10%)	8 (8%)	0.72
ICU Length of Stay (%)			
- ≤ 7 days (%)	60 (60%)	65 (65%)	0.56
- > 7 days (%)	40 (40%)	35 (35%)	0.56

Table 4 presents the results of a multivariate regression analysis assessing the factors influencing mortality in the study cohort. The analysis accounts for potential confounders, including age, comorbidities, and initial lactate levels. The regression model indicates that age ($p = 0.03$), comorbidities ($p = 0.005$), and initial lactate levels ($p < 0.001$) were significant predictors of mortality, with older age and higher lactate levels associated with increased mortality risk. However, the type of treatment (norepinephrine monotherapy vs. norepinephrine + vasopressin) did not significantly influence mortality ($p = 0.18$), suggesting that the addition of vasopressin to norepinephrine did not provide a distinct survival advantage in this cohort.

Table 4: Multivariate Regression Analysis for Mortality

Variable	Beta (95% CI)	p-value
Age	0.02 (0.01-0.04)	0.03
Comorbidities (Yes vs No)	0.15 (0.05-0.25)	0.005
Treatment (Norepinephrine + Vasopressin)	-0.08 (-0.20-0.04)	0.18
Initial Lactate Level	0.50 (0.30-0.70)	<0.001

Table 5 compares the hemodynamic parameters between the two treatment groups at 24 hours post-treatment. The data reveal that the norepinephrine + vasopressin group had a significantly higher mean arterial pressure (72.5 mmHg ± 6.1) compared to the norepinephrine monotherapy group (68.9 mmHg ± 7.3, $p = 0.02$), indicating that the combination therapy may be more effective in achieving optimal blood

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pressure control. Although the difference in lactate levels between the two groups (2.3 ± 0.7 vs. 2.0 ± 0.6) was not statistically significant (p = 0.09), both groups showed a marked reduction in lactate, reflecting improved tissue perfusion. The heart rate and central venous pressure did not differ significantly between the groups, suggesting that these parameters were similarly controlled by both treatments.

Table 5: Comparison of Hemodynamic Parameters Between Groups at 24 Hours

Parameter	Norepinephrine Monotherapy (n=100)	Norepinephrine + Vasopressin (n=100)	p-value
Mean Arterial Pressure (mmHg)	68.9 ± 7.3	72.5 ± 6.1	0.02
Heart Rate (beats/min)	96 ± 10	94 ± 8	0.21
Lactate Level (mmol/L)	2.3 ± 0.7	2.0 ± 0.6	0.09
Central Venous Pressure (mmHg)	8.2 ± 2.4	7.8 ± 2.1	0.48

Table 6 presents the analysis of organ dysfunction between the two treatment groups, focusing on renal, respiratory, and cardiovascular dysfunction. The Chi-square test reveals no significant differences between the groups in the rates of organ dysfunction, with renal dysfunction observed in 12% of the norepinephrine monotherapy group and 10% in the norepinephrine + vasopressin group (p = 0.65), respiratory dysfunction in 18% vs. 15% (p = 0.56), and cardiovascular dysfunction in 10% vs. 8% (p = 0.72). These results suggest that both treatments were similarly effective in preventing or mitigating organ dysfunction, and the addition of vasopressin did not confer a clear advantage in reducing the incidence of organ failure.

Table 6: Organ Dysfunction Analysis Between Groups (Chi-square Test)

Organ Dysfunction (n, %)	Norepinephrine Monotherapy (n=100)	Norepinephrine + Vasopressin (n=100)	p-value (Chi-square)
Renal Dysfunction (%)	12 (12%)	10 (10%)	0.65
Respiratory Dysfunction (%)	18 (18%)	15 (15%)	0.56
Cardiovascular Dysfunction (%)	10 (10%)	8 (8%)	0.72

Table 7 provides a comparative analysis of ICU length of stay and mortality rates between the two treatment groups. The mean ICU length of stay was marginally shorter in the norepinephrine + vasopressin cohort (7.8 ± 2.9 days) compared to the norepinephrine monotherapy cohort (8.2 ± 3.1 days); however, this difference did not reach statistical significance (p = 0.56). Likewise, mortality rates were similar between the groups, with 15% of patients in the norepinephrine monotherapy group and 12% in the norepinephrine + vasopressin group succumbing during the study period (p = 0.42). These findings indicate that both treatment strategies were effective in the management of hemorrhagic shock, with no significant differences observed in ICU length of stay or mortality. This reinforces the conclusion that both therapeutic regimens demonstrated comparable efficacy in terms of clinical outcomes.

Table 7: ICU Length of Stay (Days) and Mortality Comparison

Outcome	Norepinephrine Monotherapy (n=100)	Norepinephrine + Vasopressin (n=100)	p-value
ICU Length of Stay (days)	8.2 ± 3.1	7.8 ± 2.9	0.56
Mortality (%)	15 (15%)	12 (12%)	0.42

Discussion

This study conducted an in-depth assessment of the comparative effectiveness of norepinephrine monotherapy versus the combination of norepinephrine and vasopressin in the management of hemorrhagic shock. The analysis demonstrated that both therapeutic strategies markedly improved hemodynamic parameters, including mean arterial pressure, heart rate, and lactate levels. However, no statistically significant differences were identified between the two groups concerning key clinical outcomes such as mortality, organ dysfunction, or ICU length of stay. These findings highlight the comparable efficacy of the two regimens in mitigating the acute physiological disruptions associated with hemorrhagic shock.

The observed hemodynamic stabilization in both groups corroborated the established role of

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norepinephrine as a primary vasopressor in shock management. Norepinephrine's ability to increase vascular tone through alpha-adrenergic receptor activation has been widely documented Rhodes et al.(15). The addition of vasopressin, known for its vasoconstrictive effects via V1 receptor activation, appeared to enhance MAP more effectively than norepinephrine alone. However, while this slight advantage in MAP was statistically significant, it did not translate into improved survival or reduced organ dysfunction, mirroring findings from prior studies. A study by the Russellshowed that Vasopressin and Septic Shock Trial demonstrated that adding vasopressin to norepinephrine in septic shock patients did not yield a significant mortality benefit(16). This alignment suggested that the physiological benefits of vasopressin might not always lead to superior clinical outcomes.

The analysis of organ dysfunction rates further substantiated the comparable efficacy of the two treatment strategies. Both groups exhibited similar incidences of renal, respiratory, and cardiovascular dysfunction, indicating that vasopressin did not confer additional protective effects against organ failure. These findings were consistent with research by Annane et al., which showed that vasopressin's role in mitigating organ dysfunction was limited in critically ill patients(17). This similarity in outcomes highlighted that while vasopressin might improve certain hemodynamic parameters, its impact on preventing organ damage remained inconclusive in hemorrhagic shock.

Mortality rates between the two groups were also comparable, despite the hemodynamic advantages observed in the norepinephrine + vasopressin group. This lack of significant difference suggested that the addition of vasopressin did not confer a survival advantage in hemorrhagic shock. These findings aligned with studies such as De Backer et al., which reported no substantial mortality reduction with vasopressin use in shock management(18). The lack of a mortality benefit in this study could be attributed to the unique pathophysiology of hemorrhagic shock, where vasopressin's vasoconstrictive effects might not address the underlying hypovolemia as effectively as in other shock states like septic shock.

The comparison of ICU length of stay between the groups revealed no significant differences, further emphasizing the similarity in clinical outcomes. Both regimens effectively stabilized patients, reducing the need for prolonged intensive care. This finding was consistent with prior research, such as that by Martin et al., which indicated that vasopressin did not significantly impact ICU length of stay in critically ill patients(19). The comparable ICU stay durations suggested that both treatments were similarly effective in managing the acute phase of hemorrhagic shock.

Several factors could explain the lack of significant differences in clinical outcomes despite the hemodynamic improvements observed with the combination therapy. One possibility was that the study's sample size might have been insufficient to detect subtle differences in rare outcomes like mortality. Additionally, the observational nature of the study introduced potential confounding factors, such as variations in patient severity or timing of intervention, which could have influenced the results. Furthermore, the short-term focus of this study did not account for potential long-term benefits or complications associated with either treatment.

Conclusion

This study demonstrated that both norepinephrine monotherapy and the combination therapy involving norepinephrine and vasopressin were effective in achieving hemodynamic stability in patients with hemorrhagic shock. However, the addition of vasopressin did not confer a significant benefit in terms of clinical outcomes, including mortality, organ dysfunction, or ICU length of stay. These findings are consistent with existing literature, indicating that while vasopressin may enhance specific physiological parameters, its impact on improving overall clinical outcomes in the context of hemorrhagic shock appears limited. Future randomized controlled trials with larger cohorts and extended follow-up durations are essential to more comprehensively evaluate the potential therapeutic advantages of vasopressin in this setting.

References

1. Daley MJ, Lat I, Mieure KD, Jennings HR, Hall JB, Kress JP. A comparison of initial monotherapy with norepinephrine versus vasopressin for resuscitation in septic shock. Ann Pharmacother. 2013 Mar;47(3):301–10.
2. Annane D, Bellissant E, Cavaillon JM. Septic shock. Lancet Lond Engl. 2005 Jan 1;365(9453):63–78.
3. Li Y, Li H, Zhang D. Timing of norepinephrine initiation in patients with septic shock: a systematic review and meta-analysis. Crit Care. 2008;24:488.
4. Sakr Y, Reinhart K, Vincent JL, Sprung CL, Moreno R, Ranieri VM, et al. Does dopamine administration in shock influence outcome? Results of the Sepsis Occurrence in Acutely Ill Patients (SOAP) Study. Crit Care Med. 2006 Mar;34(3):589–97.
5. Ranieri VM, Thompson BT, Barie PS, Dhainaut JF, Douglas IS, Finfer S, et al. Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med. 2012 May 31;366(22):2055–64.
6. Hamzaoui O, Georger JF, Monnet X, Ksouri H, Maizel J, Richard C, et al. Early administration of norepinephrine increases cardiac preload and cardiac output in septic patients with life-threatening hypotension. Crit Care Lond Engl. 2010;14(4):R142.
7. Morimatsu H, Singh K, Uchino S, Bellomo R, Hart G. Early and exclusive use of norepinephrine in septic shock. Resuscitation. 2004 Aug;62(2):249–54.
8. LeDoux D, Astiz ME, Carpati CM, Rackow EC. Effects of perfusion pressure on tissue perfusion in septic shock. Crit Care Med. 2000 Aug;28(8):2729–32.

DOI: 10.69605/ijlbpr_13.11.2024.148

9. Kumar A, Ellis P, Arabi Y, Roberts D, Light B, Parrillo JE, et al. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. Chest. 2009 Nov;136(5):1237–48.
10. Sandifer JP, Jones AE. Is the addition of vasopressin to norepinephrine beneficial for the treatment of septic shock? Ann Emerg Med. 2013 Nov;62(5):534–5.
11. Hamzaoui O, Scheeren TWL, Teboul JL. Norepinephrine in septic shock: when and how much? Curr Opin Crit Care. 2017 Aug;23(4):342–7.
12. De Backer D, Creteur J, Preiser JC, Dubois MJ, Vincent JL. Microvascular blood flow is altered in patients with sepsis. Am J Respir Crit Care Med. 2002 Jul 1;166(1):98–104.
13. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. Open Med Peer-Rev Indep Open-Access J. 2009;3(3):e123-130.
14. Sakr Y, Dubois MJ, De Backer D, Creteur J, Vincent JL. Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. Crit Care Med. 2004 Sep;32(9):1825–31.
15. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Crit Care Med. 2017 Mar;45(3):486–552.
16. Russell JA. Vasopressor therapy in critically ill patients with shock. Intensive Care Med. 2016;45(11):1503–17.
17. Annane D, Ouanes-Besbes L, de Backer D, Du B, Gordon AC, Hernández G, et al. A global perspective on vasoactive agents in shock. Intensive Care Med. 2018 Jun;44(6):833–46.
18. De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med. 2010 Mar 4;362(9):779–89.
19. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med. 2003 Apr 17;348(16):1546–54.