https://doi.org/10.31925/farmacia.2023.6.19 **ORIGINAL ARTICLE**

EFFECT OF NOREPINEPHRINE ON HEMODYNAMICS OF SYSTEMIC CIRCULATION AND OXYGEN METABOLISM IN EMERGENCY SEPTIC SHOCK

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Manuscript received: June 2023

Abstract

The aim of this study was to analyse the value of using norepinephrine (NE) and dopamine (DA) in the clinical management of patients with emergency septic shock (SS). Eighty adult patients with SS who were treated in the hospital were included as research subjects. These patients were randomly divided into an experimental (Expt) group (NE) and a control (Ctrl) group (DA), with 40 cases per group. The hemodynamic parameters and renal function indicators of the two groups were compared. Mean arterial pressure (MAP) 1 hour and 6 hours after drug administration was significantly higher in the Expt group than after fluid resuscitation (FR). Heart rate (HR) 1 hour after drug administration was significantly lower than in the Ctrl group ($p < 0.05$). The blood lactic acid clearance rate (LCR) and peripheral vascular resistance index (PVRI) of the Expt group were significantly higher than those of the Ctrl group 1 h and 6 h after medication ($p < 0.05$). The creatinine clearance rate (CCr) and urine output (UO) of the Expt group 1 h and 6 h after liquid medication were higher than those of the Ctrl group ($p < 0.05$). Compared with DA, NE could effectively maintain hemodynamic stability, reduce blood lactic acid levels and improve renal function in patients with SS.

Rezumat

În cadrul acestui studiu ne-am propus evaluarea utilizării norepinefrinei (NE) și a dopaminei (DA) în managementul clinic al pacienților cu șoc septic (SS) de urgență. În cadrul cercetării au fost incluși optzeci de pacienți adulți cu SS, tratați în spital. Aceștia au fost împărțiți în mod aleatoriu într-un grup experimental (Expt) (NE) și un grup control (Ctrl) (DA), cu 40 de cazuri per grup. S-au urmărit valorile parametrilor hemodinamici și indicatorii funcției renale ai celor două grupuri. Presiunea arterială medie (PAM) la 1 oră și 6 ore după administrarea medicamentului a fost semnificativ mai mare în grupul Expt decât după resuscitarea fluidă. Frecvența cardiacă la 1 oră după administrarea medicamentului a fost semnificativ mai mică decât în grupul Ctrl ($p < 0,05$). Rata de eliminare a acidului lactic din sânge și indicele de rezistență vasculară periferică ale grupului Expt au fost semnificativ mai mari decât cele ale grupului Ctrl la 1 h și 6 h după administrarea medicamentelor ($p < 0,05$). Clearence-ul creatininei (CCr) și debitul urinar în grupul Expt la 1 h și 6 h după medicația lichidă au fost mai mari decât în grupul Ctrl ($p < 0,05$). În comparație cu DA, NE reduce nivelul de acid lactic din sânge, îmbunătățește funcția renală și ar putea menține în mod eficient stabilitatea hemodinamică la pacienții cu SS.

Keywords: norepinephrine, dopamine, septic shock, hemodynamics, renal function, blood lactic acid

Introduction

Septic shock (SS) is a subtype of sepsis with a mortality rate of 40 - 50%. Formerly known as infectious shock, it is defined as tissue hypoperfusion in patients, which is a state of persistent hypotension or a blood lactic acid concentration ≥4 mmol/L after volume testing [1, 2]. Gram-negative bacilli usually cause it and is mainly seen in acute purulent obstructive cholangitis, gangrenous cholecystitis, pyelonephritis, acute pancreatitis and some nosocomial infections. Symptoms include hypotension, cold, pale, clammy skin, nausea, diarrhoea vomiting and mental confusion [3-5]. The main risk factor for SS is severe sepsis with severe infection and injury [6]. Patients suspected or diagnosed of having sepsis typically present as hypotensive, tachycardic, febrile and leukocytic. As the disease progresses, signs of shock (cold skin and cyanosis) and signs of organ dysfunction (oliguria, acute kidney injury and altered consciousness) occur. However, these non-specific manifestations can be similar to many other conditions, such as pancreatitis and acute respiratory distress syndrome [7, 8]. Therefore, the diagnosis of sepsis and SS usually requires a combination of clinical findings, laboratory tests, imaging studies and physiological and microbiological data. Physicians typically make an empirical diagnosis based on a clinical presentation at the bedside or a retrospective diagnosis based on feedback from follow-up data or a significant response to antibiotic therapy.

Primary clinical interventions include opening the airway, correcting hypoxemia and establishing vascular access for early administration of fluids and antibiotics. It is recommended that immediate intravenous fluid rehydration (30 mL/kg) be started within 1 hour of onset and completed within the first 3 hours [9]. Rapid intravenous fluid rehydration is the preferred method of rehydration, and normal saline or lactated Ringer's solution is the preferred resuscitation fluid, while hypertonic starch solution is not recommended. In addition, intravenous empiric broad-spectrum antibiotics (one or more antibiotics) are clinically recommended at the optimal dose within 1 h of onset, while combined treatment with multiple antibiotics may also be considered [10-12]. In sepsis patients who remain hypotensive after adequate fluid resuscitation (FR), vasopressors are recommended and norepinephrine (NE) is the first choice. Other treatments include corticosteroids, positive inotropic therapy (dobutamine and adrenaline) and blood transfusion. Red blood cells are usually only transfused in patients with haemoglobin levels < 70 g/L [13, 14]. NE, a catecholamine, is a potent α-agonist that also stimulates β-receptors. Stimulation of α-receptors can cause extreme constriction of blood vessels, increase blood pressure and increase coronary blood flow. Activation of β-receptors increases myocardial contraction and cardiac output [15]. At a dose of 0.4 μg/kg *per* minute, based on body weight, β-receptors are predominantly activated; at higher doses, α-receptors are predominantly activated. The range of vasoconstriction induced by α-receptor activation is very wide, with skin, mucosal vessels and glomeruli being the most obvious, followed by brain, liver, mesentery and skeletal muscle. After cardiac excitation, adenosine increases among myocardial metabolites, and adenosine can promote coronary artery dilation. Clinically, NE is often administered to treat hypotension caused by acute myocardial infarction, extracorporeal circulation, pheochromocytoma resection, etc., as well as shock or hypotension caused by hypovolemia [16,17].

This suggests that SS can be managed in some ways and that NE requires further investigation. Thus, in the present study, 80 adult patients with SS, treated in the hospital from October 2020 to September 2022, were included as subjects. These subjects were divided into an experimental group (Expt) treated with NE and a control group (Ctrl) treated with dopamine (DA), with 40 cases per group. Patients' hemodynamic parameters and renal function indicators were compared between groups to analyse clinical value of NE and DA in SS emergencies.

Materials and Methods

Patients

Eighty adult patients with SS who were treated in the People's Hospital of Dongxihu District, China between 2 October 2020 and 15 September 2022 were included as research subjects. The hospital's ethics committee approved and conducted this clinical study. All these patients voluntarily participated in the study and signed an informed consent form before the study was conducted.

The diagnostic criteria for shock were as follows. (1) patients with definite symptoms of infection; (2) with systemic inflammatory response syndrome; (3) with systolic blood pressure < 90 mmHg. (4) The patients' blood pressure was maintained by infusion or medication. (5) Patients who had oliguria for more than 1 h; (6) were associated with acute delirium.

Inclusion criteria: (1) Patients were over 18 years of age. (2) Their clinical data were complete. (3) They could cooperate with the follow-up. (4) Corresponding blood pressure data could be obtained. (5) Mechanical ventilation was greater than 12 mmHg after complete FR, but vasoactive drugs were still required.

Exclusion criteria: (1) Patients died within 4 hours of admission to the ICU. (2) Patients were complicated by acute myocardial infarction; (3) or severe mitral valve disease. (4) Patients were associated with pleural effusion; (5) and complicated by massive pulmonary embolism.

Pre-treatment processing methods

Patients were admitted to the intensive care unit, baseline data such as age and sex were collected, and the physiological and pathological conditions of the patients were assessed. Non-invasive mean arterial pressure (MAP), cardiac output (CO), heart rate (HR) and central venous pressure were measured.

The eighty patients were randomly divided into Expt group and Ctrl group with 40 cases per group. The Expt group received NE drugs while the Ctrl group received DA drugs. In the Expt group, there were 24 male and 16 female patients, aged 20 - 65 years, with a mean age of 50.48 ± 7.15 years. In the Ctrl group, there were 22 male and 18 female patients aged 21 - 64 years, with a mean age of 52.06 ± 6.88 years. There was no significant difference in the number of male and female cases and their ages between the groups ($p > 0.05$), indicating comparability.

Treatment methods

Patients were examined by non-invasive hemodynamic, and full FR and vasoactive medication were given in accordance with clinical guidelines for the treatment of severe sepsis and SS. However, all the patients did not take glucocorticoids. If the MAP of a patient was ≥ 65 mmHg and the UO (urine output) was ≥ 0.15 mL/(kg*h), resuscitation could be considered to be up to standard within 6 h of initial treatment. For patients with hypovolemia, fluid challenge therapy was administered with 400 mL of colloidal solution used within 30 min of the initial treatment. Patients with organ hypoperfusion needed to be treated with faster and higher doses of fluid therapy.

For vasoactive drugs, the dose of NE was 0.1 μg/(kg*min) (Sichuan Pharmaceutical Preparations Co., Ltd., China), while the dose of DA was 6 - 24 μg/(kg*min) (Sichuan Pharmaceutical Preparations Co., Ltd., China), and the dose of DA was increased every 2 min.

Observation indicators

The aetiology of the patients was recorded and included severe pneumonia, severe trauma with infection, diabetic ketoacidosis with infection, biliary tract infection, intracranial infection and severe pancreatitis with infection.

CSM3100 non-invasive hemodynamic detection system (Shenzhen General Meditech Inc., China) was applied for non-invasive hemodynamic detection of the patients. The patients were in the supine position, the bilateral neck and chest were wiped with ethanol, and 4 electrodes were affixed to the positions on the neck at ear lobe level on both sides. Then 4 more electrodes were attached to the bilateral chest, on the midaxillary line horizontal to the xiphoid process. The hemodynamic indicators, including MAP, HR, CO, peripheral vascular resistance index (PVRI) and arterial lactic acid clearance rate (LCR), were monitored after FR (T0), 1 h after medication (T1) and 6 h after medication (T2).

Renal function indicators, including UO and creatinine clearance rate (CCr), were determined at T0, T1 and T2. The creatinine levels were determined using an automated analyser (BS-2800M Mindray Medical Electronics Co., Shenzhen, China).

Statistical analysis

The research data were processed and analysed using SPSS19.0 (IBM, USA), with measurement data described in mean ± standard deviation, while enumeration data in percentage (%). Analysis of variance for repeated measurement was used for inter-group comparisons and two-factor analysis of variance was adopted for intra-group comparisons. A difference was recognized to be statistically significant as $p < 0.05$ in a bilateral test.

Results and Discussion

Comparison of aetiologies between groups

As displayed in Figure 1, the Expt group included 23 cases of severe pneumonia, 7 cases of severe trauma with infection, 5 cases of diabetic ketoacidosis with infection, 3 cases of biliary tract infection, 2 cases of intracranial infection and 1 case of severe pancreatitis with infection. In the Ctrl group, 22 cases had severe pneumonia, 8 cases had severe trauma with infection, 4 cases had diabetic ketoacidosis complicated with infection, 3 cases had biliary tract infection, 2 cases had intracranial infection and 1 case had severe pancreatitis complicated with infection. There was not any significant difference in the number of cases suffering from severe pneumonia, severe trauma with infection, diabetic ketoacidosis with infection, biliary tract infection, intracranial infection and severe pancreatitis with infection between the Expt group and Ctrl group ($p > 0.05$).

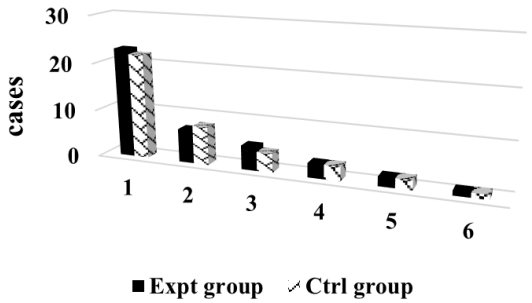

Figure 1.
Comparison of aetiologies between groups 1-6: severe pneumonia, severe trauma with infection, diabetic ketoacidosis with infection, biliary tract infection, intracranial infection and severe pancreatitis with infection, respectively

Comparison of hemodynamic indicators before and after treatment between groups

In the Expt group, the MAP was 54.38 ± 10.13 mmHg at T0, 85.91 ± 12.44 mmHg at T1 and 95.21 ± 10.67 mmHg at T2, while HR was 122.41 ± 12.16 beats/min at T0, 113.38 ± 11.88 beats/min at T1 and 110.44 ± 11.47 beats/min at T2 (Figure 2A). In Ctrl group, the MAP was 55.09 ± 11.43 mmHg at T0, 83.33 ± 10.29 mmHg at T1 and 89.64 ± 12.02 mmHg at T2, while HR was 120.85 ± 13.02 beats/min at T0, 141.06 ± 13.62 beats/min at T1 and 109.52 ± 12.77 beats/min at T2 (Figure 2B).

After comparison, MAPs after FR, 1 h after medication and 6 h after medication in Expt group were not significantly different from those in Ctrl group ($p > 0.05$). There was not any significant difference in HR after FR ant 1 h and 6 h after medication between groups ($p > 0.05$). The MAPs 1 h and 6 h after medication in Expt group were much higher than those after FR, with statistically significant differences ($p < 0.05$). The HR of Expt group 1 h after medication was remarkably lower than that of Ctrl group ($p < 0.05$).

The LCR of Expt group was 18.33 ± 4.25%, 34.71 ± 7.22% and 43.88 ± 8.04% at T0, T1 and T2, respectively. In Ctrl group, LCR was 20.21 ± 3.92%, 23.09 ± 6.92% and 31.65 ± 7.43% at T0, T1 and T2, respectively (Figure 3).

The LCRs of Expt group 1 h after medication and 6 h after medication were significantly higher than that after FR ($p < 0.05$). The LCR of Expt group was considerably higher than that of Ctrl group 1 h and 6 h after medication ($p < 0.05$).

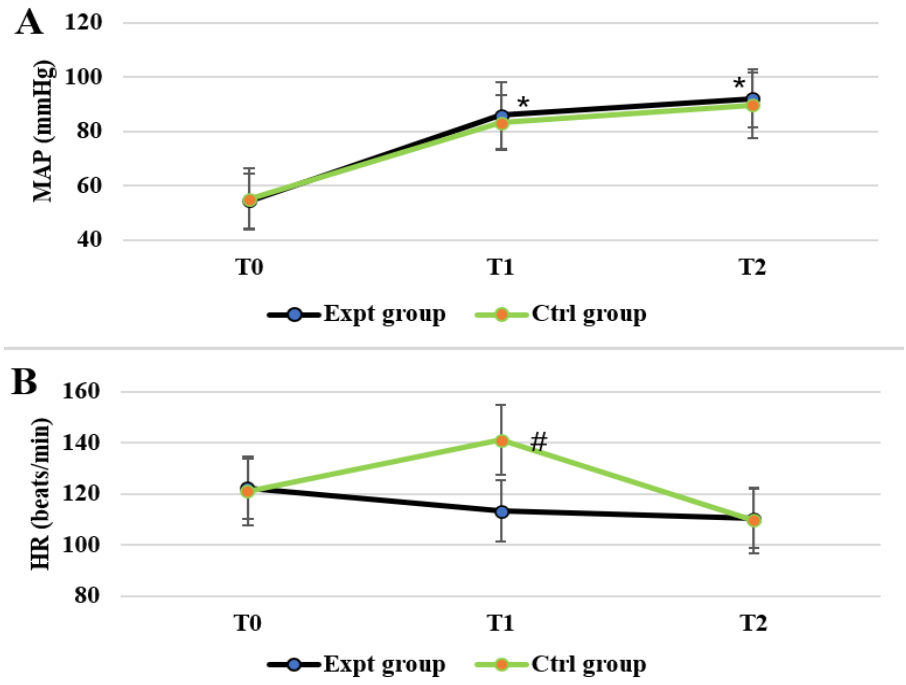

Figure 2.

Comparison of MAP and HR before and after treatment between groups; A represented MAP; B stood for HR

* indicated that there were significant differences between T1, T2 and T0 ($p < 0.05$)

indicated significant difference between Expt and Ctrl groups ($p < 0.05$)

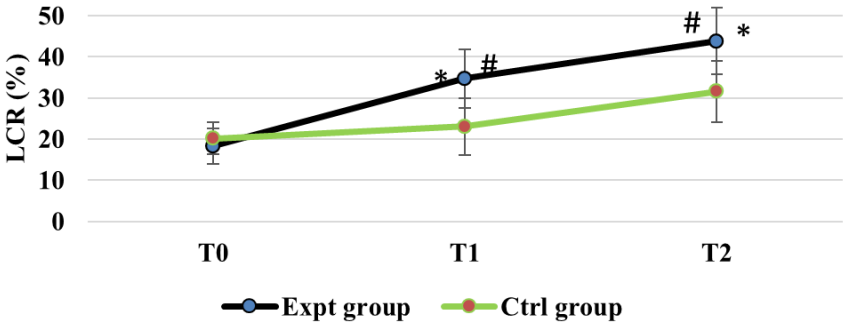

Figure 3.

Comparison of LCR before and after treatment between groups

* meant that there were significant differences at T1 and T2 compared with T0 ($p < 0.05$)

marked statistically significant differences as well between Expt and Ctrl groups ($p < 0.05$)

In Figure 4, the PVRI of Expt group was 51.75 ± 8.23, 108.33 ± 12.05 and 127.63 ± 18.42% at T0, T1 and T2, respectively. In Ctrl group, the PVRI was 50.31 ± 9.11, 63.82 ± 10.34 and 91.77 ± 15.62 at T0, T1 and T2, respectively.

PVRIs at 1 h and 6 h after medication were notably higher than that after ($p < 0.05$). The PVRI in Expt was considerably higher than that in Ctrl group 1 h and 6 h after medication ($p < 0.05$).

As displayed in Figure 5, the CO reached 5.52 ± 1.03, 5.29 ± 0.75 and 5.07 ± 1.12 at T0, T1 and T2, respectively in Expt group. The CO in Ctrl group was 5.35 ± 1.15, 5.37 ± 1.11 and 5.16 ± 0.83 at T0, T1 and T2, respectively.

No significant differences were discovered in CO 1 h and 6 h after medication compared with that after FR in both groups ($p > 0.05$). There was also no significant difference in CO between Expt group and Ctrl group after FR, 1 h after medication, as well as 6 h after medication ($p>0.05$).

The CCr was 30.46 ± 7.22% at T0, 69.11 ± 10.44% at T1 and 99.52 ± 12.06% at T2 in Expt group (Figure 6). In Ctrl group, the CCr was 32.11 ± 8.07%, 45.58 ± 7.17% and 85.77 ± 11.31% at T0, T1 and T2, respectively (Figure 6).

The CCr 1 h after medication and 6 h after medication was significantly higher than that after FR in both groups ($p < 0.05$). The CCr of Expt group was significantly higher than that of Ctrl group 1 h after liquid medication and 6 h after medication ($p < 0.05$).

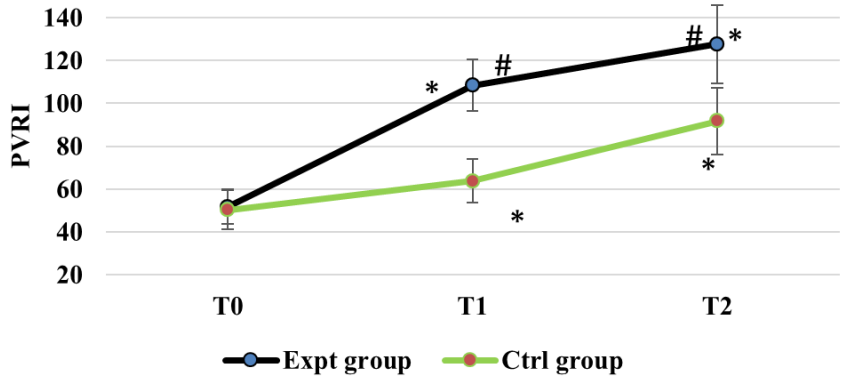

Figure 4.
Comparison of PVRI between groups before and after treatment
* marked significant differences at T1 and T2 compared to T0 ($p < 0.05$)
# marked statistically significant differences between Expt and Ctrl groups ($p < 0.05$)

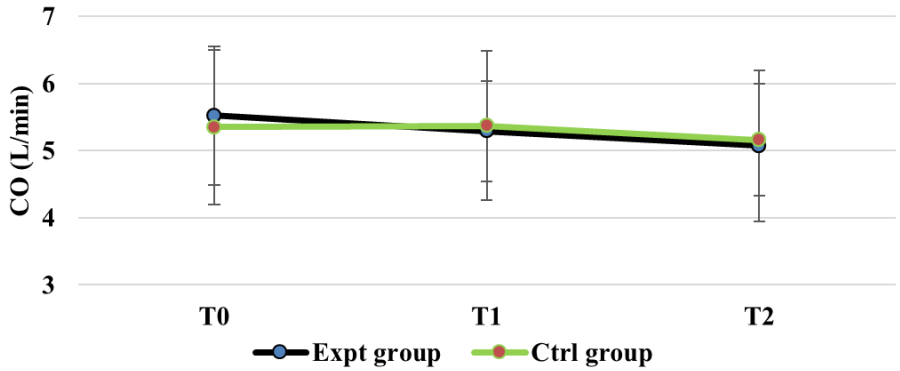

Figure 5.
Comparison of CO before and after treatment between groups

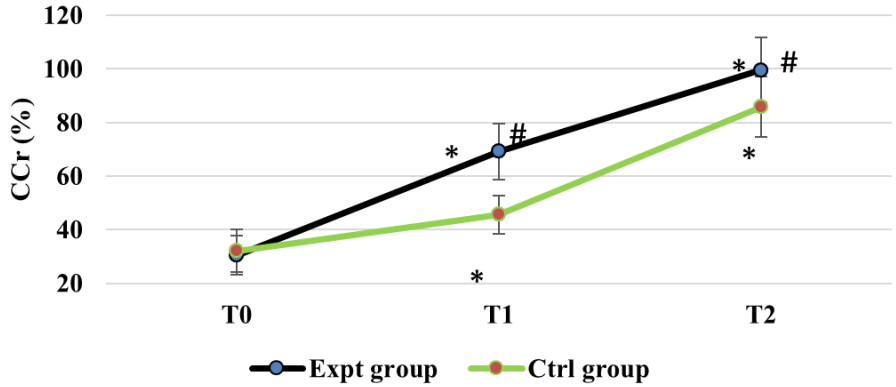

Figure 6.
Comparison of CCr before and after treatment between groups.
* marked significant differences at T1 and T2 compared with T0 ($p < 0.05$)
# marked statistically significant differences as well between groups ($p < 0.05$)

UO reached 24.19 ± 6.33 mL/(kg*h) at T0, 138.42 ± 23.14 mL/(kg*h) at T1 and 180.05 ± 19.05 mL/(kg*h) at T2 in Expt group (Figure 7). The UO in Ctrl group reached 23.55 ± 4.95 mL/(kg*h), 46.03 ± 10.05 mL/(kg*h) and 99.71 ± 21.15 mL/(kg*h) at T0, T1 and T3, respectively (Figure 7).

The UOs 1 h and 6 h after medication were much higher than that after FR in both groups ($p < 0.05$). The UO in Expt group was higher than that in Ctrl group 1 h and 6 h after liquid medication, showing significant differences ($p < 0.05$).

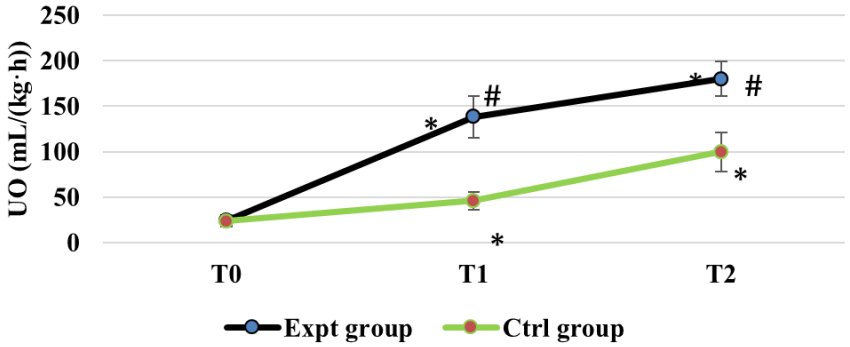

Figure 7.
Comparison of UO before and after treatment between groups
* indicated that there were significant differences at T1 and T2 compared to T0 ($p < 0.05$)
# represented statistically significant differences as well between groups ($p < 0.05$)

SS is a specific form of severe sepsis associated with persistent hypotension that can't be corrected by adequate fluid resuscitation [18]. Clinical examples include pneumonia, peritonitis, cholangitis, urinary tract inflammation, cellulitis, meningitis and abscesses. SS should be treated as a medical emergency like stroke and acute myocardial infarction, requiring rapid identification, appropriate antibiotics, careful hemodynamic support and control of the source of infection [19-21]. Currently, there is no convincing evidence to support other drugs for the first-line treatment of SS and NE remains the preferred vasopressor to achieve target MAP [22]. Therefore, 80 adult patients with SS who were treated in the hospital from 2 October 2020 to 15 September 2022 were enrolled as research subjects in this study. These patients were randomly divided into Expt group (NE) and Ctrl group (DA), with 40 cases per group. In terms of aetiology, there was no significant difference in the number of cases of severe pneumonia, severe trauma with infection, diabetic ketoacidosis with infection, biliary tract infection, intracranial infection and severe pancreatitis with an infection between groups ($p > 0.05$). This provided a basis for subsequent hemodynamic analysis.

Non-invasive haemodynamic can measure cardiac preload and fluid volume to guide clinical adjustment of the treatment plan, with remarkable results. This work found that the MAP 1 h and 6 h after medication in the Expt group was significantly higher than that after while the HR 1 h after medication was quite lower than that of the Ctrl group. These results were similar to those obtained by Menif *et al*. (2011) [23]. It was suggested that compared with DA, NE could effectively improve patients' MAP and HR, thus maintaining patients' hemodynamic stability. The serum LCR at 1 h and 6 h after administration in the Expt group was much higher than that in the Ctrl group. This suggested that NE could effectively reduce the blood lactic acid level in SS patients. PVRI is a parameter that reflects cardiac afterload and is positively correlated with the increase in peripheral resistance [24, 25]. The results showed that the PVRI of the Expt group was significantly higher than that of the Ctrl group at 1 h and 6 h after drug administration, indicating that NE could effectively promote myocardial contraction and increase blood oxygen demand in SS patients. The CCR and UO of the Expt group 1 h and 6 h after liquid medication were higher than those of the Ctrl group. CCr mainly reflects the ability of the kidneys to remove toxins (creatinine). In the early stages of nephropathies, CCr is the first to decline. When CCr drops to 50%, only the blood creatinine level is abnormal. These results showed that NE could effectively improve renal function in patients with SS compared to DA.

Conclusions

The study included 80 cases of adult patients suffering from SS treated in the hospital between 2 October 2020 and 15 September 2022. The subjects were randomly divided into Expt group (NE) and Ctrl group (DA), with 40 cases per group. The hemodynamic parameters and renal function indicators of the patients in the two groups were compared. Compared with DA, NE could effectively maintain the hemodynamic stability of patients with SS, reduce the level of lactic acid in the blood and improve the renal function of patients. However, this work had some limitations, such as a small sample size of patients from the same hospital and no follow-up of patients' prognosis. Therefore, a large number of adult patients with SS should be re-included in future studies to further analyse the clinical effect of NE. In conclusion, this study provides a reference for drug therapy in patients with SS.

Conflict of interest

The authors declare no conflict of interest.

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