Effects of vasoactive drugs on hepatic and intestinal circulation and intestinal barrier in patients with septic shock

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ABSTRACT

In this study, 60 patients with septic shock were selected over the course of 1 year, and the effects of dopamine and norepinephrine combined with dobutamine on hepatic and intestinal circulation and intestinal barrier in patients with septic shock were studied by comparison between the control group and the experimental group. All patients received mechanical ventilation to maintain breathing at 14 to 20 times/min. The experimental group was treated with vascular active drugs after adequate rehydration, and the control group only received adequate rehydration. There were extremely significant differences ($p<0.01$) in the total effective rate of each group. There were significant differences in the hemodynamic indexes in each group ($p<0.05$). There was a significant difference in total 24-hour bile output ($p<0.01$). There were significant differences in liver function and blood lipid values in patients ($p<0.01$). There were significant differences in the repair of epithelial injury at 0 hour, 48 hours and 96 hours ($p<0.01$). There were significant differences in the transmembrane resistance of monolayer cells ($p<0.01$). The expression differences of three proteins ZO-1, occludin and β-actin were also significant, among which the three proteins in the control group were weak, while those in groups A and B were strong. The expression of tight junction protein in monolayer cells was weakly positive in expression and strong in other proteins. In conclusion, vasoactive drugs had significant effects on hepatic and intestinal circulation and intestinal barrier in patients with septic shock.

Significance of this study

What is already known about this subject?

► Septic shock causes death in severe cases, and reducing the death rate is one of the current pressing clinical issues. Hepatic and intestinal circulation form bile after the transformation of vasoactive drugs through the liver.

What are the new findings?

► Vasoactive drugs have a definite effect on septic shock clinically. Therefore, it is of great importance to study the effect of vasoactive drugs on hepatic and intestinal circulation and intestinal barrier function of patients with shock.

How might it impact on clinical practice in the foreseeable future?

► This study can provide a theoretical basis for widening the range of use of vasoactive substances and lay an important theoretical foundation for other studies.

INTRODUCTION

Over the recent years, the incidence of septic shock has gradually increased. Septic shock causes death in severe cases, and reducing the death rate is one of the current pressing clinical issues.[1–3] Studies have shown that rational choice of appropriate treatment method and vasoactive drugs, which can improve the blood pressure and oxygen level of patients significantly, are effective in treating this disease. Dopamine and norepinephrine combined with dobutamine are commonly used therapeutic drugs, which can improve the cardiac function of patients.[4–7] Hepatointestinal circulation refers to the phenomenon that drugs are discharged into the intestinal tract through bile or part of the bile, and then reabsorbed in the intestinal tract and returned to the liver via the portal vein. As an important circulating tissue in the body, hepatic and intestinal circulation form bile after the transformation of vasoactive drugs through the liver. The intestinal tract is the main place for digestion and absorption of nutrients, and also the innate barrier to ensure the homeostasis of the body's internal environment. On the one hand, the growth of the body requires the intestinal tract to maintain a certain permeability to ensure that nutrients can be absorbed and used to the maximum extent. On the other hand, the health of the body requires the intestinal tract to maintain integrity to prevent harmful substances such as pathogens and toxins from entering the body through the intestinal tract, so as to play a barrier function, including physical screens, barriers, chemical barriers, microbial barriers and immune barriers. As an important organ in the body, the intestinal tract can protect

the normal circulation of the body by preventing harmful substances from entering the body.[8–11] Therefore, the intestinal tract is important in studying the effect of vasoactive drugs on hepatic and intestinal circulation and intestinal barrier in patients with septic shock.

MATERIALS AND METHODS

General information

This study was conducted between September 2017 and September 2018. Sixty patients with septic shock were included, with 30 male and 30 female patients and a mean age of 30–70 years. The control group included patients with septic shock but who did not receive vasoactive drugs. Patients in the experimental group received dopamine (group A) or norepinephrine plus dobutamine (group B).

METHODS

Groups

Both the control group and the experimental group received mechanical ventilation to maintain respiration at 14–20 times/min. The experimental group received vasoactive drugs after adequate fluid infusion, while the control group only received adequate fluid infusion. Then, all the patients were observed and compared.

Observation indexes and methods

Clinical outcomes

Clinical outcomes included very effective, effective and ineffective treatment. Treatment was considered very effective when the patient's systolic blood pressure (SBP) rose to 10.7 kPa or increased to more than 4.00 kPa within 12 hours of drug therapy, and the patient gradually regained his or her consciousness, respiratory changes were common and urine volume increased. Treatment was considered effective when SBP only rose to >10.7 kPa or more than 4.00 kPa within 12 hours to 24 h after drug treatment. The patient gradually regained consciousness, with respiratory changes and increased urine volume. Treatment was considered ineffective when SBP remained below 10.7 kPa or 4.00 kPa after 24 hours of drug administration, and clinical symptoms were not relieved.

Indexes of hemodynamic observation in each group were compared

Hemodynamic indexes were observed in all patients, including SBP, diastolic blood pressure (DBP), mean arterial pressure (MAP) and peak left ventricular pressure (PLVS).

Total bile output was 24 hours in each group

The patients were administered by gavage with a concentration of 12 mg/kg xx, and the bile was collected for 24 hours by drainage, and the volume was measured one by one.

Bile was excreted within 24 hours at each time point for each group

All patients were given by gavage with a concentration of 12 mg/kg xx, and bile excretion was calculated for 0–2 hours, 2–4 hours, 4–6 hours, 6–8 hours, 8–10 hours, 10–12 hours and 12–24 hours, respectively.

Comparison of liver function and blood lipid values in each group

Liver function (ALT, AST) and blood lipids (TG, TC, FFA) were compared in each patient.

Scratch test of epithelial cells

Large intestine epithelial cells from each patient were cultured until the cells grew into dense monolayers, and then the cultured cells were scraped along the culture dish with a sterile Pipette tip. The wound width of the monolayer cells at 0 hour, 48 hours and 96 hours was observed under the microscope.

Comparison of monolayer cell barrier function in each group

The transmembrane resistance values of the monolayer cells were measured at 0, 3, 9 and 12 hours by a resistivity instrument, and cellular proteins were extracted after the experiment for Western blotting assays.

Effects of tight lignin expression in monolayer cells in each group

Colon epithelial cells from each patient were cultured for 12 hours, and protein was collected for Western blotting assays.

Effects of monolayer cells on bacterial adhesion and invasion in each group

All patients were cultured for 12 hours in the cell culture box, and non-adherent and invasive bacteria were washed off by PBS, which contained Triton X-100. Cells were collected and cultured in the biochemical culture box for 16 hours, and the number of colonies was counted.

Correlation analysis of efficacy of vasoactive drugs and patients with septic shock

According to the results of the aforementioned experiments, the correlation between vasoactive drugs and outcome of patients with septic shock was analyzed.

Statistical method

SPSS V.20.0 software was used for statistical analysis. All experimental data were represented by mean±SD ($\bar{x}$ ±s), and univariate analysis of variance was used for statistical analysis of data between the two groups.

RESULTS

Clinical outcomes

There were significant differences in the total effective rate of each group ($p<0.01$). There were also significant differences in the number of patients whose clinical outcome was very effective and those whose clinical outcome was ineffective ($p<0.01$). Meanwhile, there was no difference in the number of patients whose clinical outcome was effective among the groups ($p>0.05$). Therefore, the results indicated that dopamine and norepinephrine combined with dobutamine had a significant therapeutic effect on patients with septic shock (table 1).

Table 1 Therapeutic outcomes of each group

Group	n	Very effective	Effective	Ineffective	Effectiveness rate (%)
A	20	18	1	1	95
B	20	17	2	1	95
Control	20	6	2	12	40
P value	–	0.006	0.125	0.001	0.001

Indexes of hemodynamic observation in each group

There were significant differences in the hemodynamic indexes in each group, among which there were significant differences in SBP, DBP and MAP. Significant difference was observed in PLVS ($p<0.05$) (table 2).

Total 24-hour bile output in each group

There was a significant difference in the total bile output of patients within 24 hours in each group ($p<0.01$). The total bile output was 17.88%, 18.35% and 40.25% for group A, group B and the control group, respectively (table 3).

Bile excretion within 24 hours at each time point in each group

There were significant differences in the concentration of bile output in each group within 24 hours ($p<0.05$). Significant difference was observed in the 0–2, 2–4, 4–6, 6–8 and 10–12 hour bile excretion ($p<0.01$), and in the 8–10 and 12–24 hour bile excretion ($p<0.05$) (table 4).

Comparison of liver function and blood lipid values in each group

There were significant differences in liver function and blood lipid values in each group ($p<0.01$). There were significant differences in liver function (ALT and AST) and blood lipid values (TG, TC and FFA) in each group ($p<0.01$) (table 5).

Comparison of repair of epithelial cell injury in each group

There were significant differences in the repair of epithelial cell injury at 0, 48 and 96 hours in each group ($p<0.01$) (online supplemental table 1).

Comparison of monolayer cell barrier function in each group

There were significant differences in the transmembrane resistance (TER) of monolayer cells in each group ($p<0.01$). Among them, group A and group B showed an attenuating effect on the decline of monolayer cell TER. Meanwhile, the control group showed a significant downward trend compared with group A and group B (online supplemental table 2).

There was significant difference between the TER of monolayer cells in each group. There were also significant differences in the expression of ZO-1, occludin and β-actin, among which the three proteins in the control group were weak while those in groups A and B were strong (online supplemental tables 3 and 4).

Table 2 Indexes of hemodynamic observation in each group

Group	n	SBP	DBP	MAP	PLVS
A	20	59.06±10.25	35.26±6.87	50.26±3.56	71.05±6.58
B	20	56.25±9.87	38.98±8.74	52.46±6.54	74.35±8.97
Control	20	48.25±12.35	29.54±8.74	42.56±9.87	62.15±3.56
P value	–	0.005	0.004	0.005	0.012

DBP, diastolic blood pressure; MAP, mean arterial pressure; PLVS, peak left ventricular pressure; SBP, systolic blood pressure.

Table 3 Total 24-hour bile output in each group

Group	A	B	Control	P value
n	20	20	20	–
Total bile output	17.88	18.35	40.25	0.005

Effects of tight junction protein expression in monolayer cells in each group

The expression of tight junction protein in monolayer cells was detected by Western blotting assays, in which ZO-1 was weakly positive while other proteins were strongly positive (online supplemental figure 1).

Effects of monolayer cells on bacterial adhesion and invasion in each group

There was a significant difference between the statistics of anti-bacterial adhesion of monolayer cells in each group and the number of invaded colonies ($p<0.01$). The number of colonies was 1.7×10^4, 1.8×10^4 and 3.2×10^4 in the control group, respectively. Therefore, the results indicated that the monolayer cells of patients with septic shock treated with dopamine and norepinephrine combined with dobutamine were significantly resistant to bacterial adhesion and invasion (online supplemental table 5).

Correlation analysis of efficacy of vasoactive drugs and patients with septic shock

The scatter plot shows the distribution of correlation between the efficacy of vasoactive drugs and the outcome of patients with septic shock. It can be seen from online supplemental figure 2 that the efficacy of the vasoactive drugs and the outcome of patients with septic shock in each group showed a linear correlation.

DISCUSSION

Septic shock is often caused by acute infection. Studies have found that the pathogenesis of septic shock is mainly caused by ischemia and hypoxia of tissues and organs. As the main method to treat this disease, vasoactive drugs have been used in more and more patients.[12–15] In recent years, dopamine and norepinephrine in combination with dobutamine have

Table 4 Bile excretion within 24 hours at each time point in each group

Group	n	0–2 hours	2–4 hours	4–6 hours	6–8 hours	8–10 hours	10–12 hours	12–24 hours
A	20	1.78	1.63	1.25	1.89	1.75	0.85	0.54
B	20	1.64	1.42	1.17	1.68	1.54	0.73	0.38
Control	20	7.84	6.58	6.02	7.12	6.74	4.58	2.05
P value	–	0.005	0.001	0.005	0.004	0.010	0.003	0.012

Table 5 Comparison of liver function and blood lipid values in each group

Group	n	ALT	AST	TG	TC	FFA
A	20	109.96±23.15	59.64±21.24	2.73±0.58	5.48±1.25	0.53±0.05
B	20	107.25±24.12	54.25±15.24	2.65±0.35	5.47±1.34	0.51±0.09
Control	20	99.87±12.35	47.56±12.56	2.31±0.25	4.36±0.58	0.46±0.03
P value	–	0.005	0.002	0.006	0.004	0.002

ALT, alanine aminotransferase; AST, aspartate transaminase; FFA, free fatty acid; TC, total cholesterol; TG, triglyceride.

been used clinically.[16] Therefore, it is of great importance to study vascular active drugs in patients with septic shock enterohepatic circulation and the influence of the intestinal barrier, which could provide a scientific theoretical basis for clinical application of vascular active drugs, and at the same time lay a theoretical foundation for future studies. In this study, 60 patients with septic shock were selected within 1 year, and the effects of dopamine and norepinephrine combined with dobutamine on hepatic and intestinal circulation and intestinal barrier in patients with septic shock were studied by comparing the control group and the experimental group. The results showed that the curative effect of total effective groups of patients was significantly different. There were significant differences in the hemodynamic indexes in each group. There were significant differences in total bile output. Among them, bile output at 0–2, 2–4, 4–6, 6–8 and 10–12 hours showed significant differences while bile output at 8–10 and 12–24 hours had significant differences. There were significant differences in liver function and blood lipid values in patients. There were significant differences in the repair of epithelial injury at 0, 48 and 96 hours. There were significant differences in the TER of monolayer cells. The expression differences of ZO-1, occludin and β-actin were also significant; the three proteins were weakly expressed in the control group but strongly expressed in groups A and B. The monolayer cells of patients with septic shock treated with dopamine and norepinephrine combined with dobutamine showed significant resistance to bacterial adhesion and invasion. The correlation analysis of efficacy of the vasoactive drugs and patients with septic shock showed a linear distribution, showing a certain correlation.

The results also showed that rational selection of drugs for treating the symptoms of patients with septic shock is of great significance for the rehabilitation of patients and has a good effect on improving the circulation of patients.[17–19] Heptametric circulation is an important circulation channel in the body. The metabolism of bile has a scientific guiding role in investigating the efficacy of drugs.[20 21] Intestinal barrier function mainly includes mechanical barrier, chemical barrier, immune barrier and biological barrier.[22] Histological observation of the intestinal mucosa is most commonly used to study its function,[23] which can prevent the invasion of intestinal bacteria and protect the health and normal function of the body.[24 25] By studying blood pressure and oxygen transport level of patients treated with vasoactive drugs, it is of great significance to improve the cardiac function of patients with septic shock. Dopamine and norepinephrine combined with dobutamine can increase the circulation of patients and also improve the cardiac function of patients. Comprehensive treatment measures, and identification of the causes of the disease and the best treatment methods reduce the physical and mental pain of patients to the greatest extent, and have a good effect on the timely recovery and subsequent recovery of the patients.

Levosimendan was also used in patients with infectious diseases. Sepsis-related myocardial inhibition is called septic cardiomyopathy. When septic shock occurs, the fatality rate is up to 50∼70%. With the popularization of bedside color Doppler ultrasound, the awareness and attention to the stress myocardium caused by infection are gradually increased, and timely symptomatic treatment is very important. Levosimendan is a new cardiac drug and a Ca^{2+} sensitizer. Its sensitization effect does not affect the concentration of intracellular Ca^{2+}, does not cause arrhythmias due to intracellular Ca^{2+} overload, does not increase the transport energy of intracellular Ca^{2+}, and does not cause increased myocardial oxygen consumption and sympathetic activation. The researchers believe that stabilizing hemodynamics in patients with sepsis should improve liver function, which will be further explored in future studies.

To sum up, vasoactive drugs have a definite effect on septic shock clinically. Therefore, it is of great importance to study the effect of vasoactive drugs on hepatic and intestinal circulation and intestinal barrier function of patients with shock. At the same time, this study can provide a theoretical basis for widening the range of use of vasoactive substances and lay an important theoretical foundation for other studies.

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