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Effects of dopamine, norepinephrine and dobutamine on gastric mucosal pH of septic shock patients

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Abstract. The effect of different vasoactive drugs on the pH [intracellular pH (pH_i)] of gastric mucosa in patients with septic shock was evaluated in the present study. According to the vasoactive drugs applied, 48 patients with septic shock were divided into 3 groups: A, B and C, with 16 cases each. Cases of group A were treated with dopamine, those of group B with norepinephrine while those of group C were treated with norepinephrine plus dobutamine. The changes of pH of gastric mucosa were observed before treatment (baseline) and 6, 12, 24 and 48 h after treatment, and the hemodynamic indicators were observed before treatment (baseline) and 6 h after administration. The gastric mucosal pH was not significantly different between two of the three groups before treatment (each at P>0.05). The gastric mucosal pH of group A did not change 6, 12, 24 and 48 h after treatment with drugs compared with the baseline (all at P>0.05), while the gastric mucosal pH in groups B and C were each statistically higher at the time points of 6, 12, 24 and 48 h after treatment with drugs compared with the respective baselines (all at P<0.05). Following treatment with drugs, the gastric mucosal pH of group C at all the time points of 6, 12, 24 and 48 h after treatment were significantly higher than those of groups A and B at the same time points after treatment, while there were some statistical differences between groups A and B at these time points (6, 12, 24 and 48 h after treatment; P<0.05). The hemodynamic indicators of the patients before treatment were not significantly different between two of the three groups (all at P>0.05). Compared with the baseline values, the mean arterial pressure and the cardiac index of each group after treatment were significantly increased, the pulmonary capillary wedge pressure and the central venous pressure of groups B and C significantly increased (all at P<0.05) and the heart rate of group A was significantly increased (P<0.05). In conclusion, the gastric mucosal pH of the septic shock patients was increased when treated with norepinephrine or with dobutamine. Additionally, the gastric mucosal pH was significantly higher when the patients were treated with dobutamine and norepinephrine in combination than with norepinephrine or dopamine alone. Dopamine, norepinephrine and dobutamine can improve the systemic hemodynamic conditions in patients with septic shock.

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Introduction

Septic shock is a disease caused by infection, with abnormal blood distribution as the main feature, and with the hypoxic ischemic tissues and organs as the major pathophysiological changes (1-3). The gastrointestinal hypoxia remains after the blood pressure is corrected. The early monitoring of gastric pH can be useful in the diagnosis of the local tissue hypoperfusion and hypoxia, and application in clinical medication (4,5). Treatment with vasoactive drugs is an effective means of relieving ischemia and hypoxia in tissue and organs.

In the present investigation, of 48 cases with septic shock, the gastric mucosal pH was monitored when patients were treated either with dopamine or norepinephrine alone or with norepinephrine and dobutamine in combination to observe the effects of vasoactive drugs on gastric pH (6).

Materials and methods

Clinical data. From July 2002 to December 2006, in total 48 cases, including 32 males and 16 females aged 15-83 years at an average of 48.9 years, were hospitalized and treated with vasoactive drugs for >2 days at the People's Hospital of Lishui City (Zhejiang, China). Primary disease included 18 cases of severe pulmonary infection, 12 cases of abdominal infection, 2 cases of skin avulsion plus infection in a large surface, 6 cases of severe pancreatitis, and 5 cases of acute suppurative cholangitis. Two cases of lower limb infection, and 3 cases of

thoracoabdominal injuries caused by traffic accidents. The 48 cases were divided into 3 groups, and the gender, age, acute physiology, and chronic health evaluation, hemodynamic indicators and gastric pH prior to treatment were not significantly different between the 2 groups (all at P>0.05).

The diagnostic criteria employed for septic shock were: i) Patient with clear infected lesions; ii) patients with systemic inflammatory response; iii) systolic blood pressure of <90 mmHg (1 mmHg=0.133 kPa), or a decrease in the systolic blood pressure by 40 mmHg from the original base that did not recover after 1 h of fluid resuscitation, or decreased systolic blood pressure recovered and maintained normal only after the patients were treated with vasoactive drugs; and iv) patients with poor perfusion in tissues. The patients who met the above criteria were divided into 3 groups and treated with different vasoactive drugs. In group A, 16 patients were treated with dopamine (3-15 μg/kg/min). In group B, norepinephrine (0.05-0.50 μg/kg/min) was used to treat 16 patients. Group C comprised 16 patients who were treated with dobutamine (2-5 μg/kg/min) plus norepinephrine. The mean arterial pressure (MAP) of the 3 groups of patients was at 70-80 mmHg for regulating standards, and the patients were treated with adequate fluid resuscitation before medication.

Observation index. i) A catheter was surgically arranged in the radial artery to continually monitor the arterial pressure and arterial blood gas analysis; ii) a floating catheter was inserted into the right internal jugular vein to monitor the pulmonary capillary wedge pressure (PAWP), the cardiac output (CO), and the central venous pressure (CVP); iii) a gastric tension tube (TRI16 F; Datex-Ohmeda, Helsinki, Finland) was set through the nose to measure the carbon dioxide partial pressure within the gastric mucosa ($PiCO_2$), and the pH of gastric mucosa was calculated according to the Henderson-Hasselbalch equation, pH=6.1 l g [HCO-3]/$PiCO_2$ x 0.03; and iv) the pH of gastric mucosa prior to medication (baseline) and 6, 12, 24 and 48 h after administration of hemodynamic changes of each group were observed, and the hemodynamic changes at 6 h in each group were observed after treatment.

Statistical analysis. Data were presented as mean ± standard deviation, processed with SPSS 11.0 software (IBM Corp., Armonk, NY, USA) and all treatments were subjected to variance analysis. The intergroup statistical results were compared using the q test and P<0.05 was considered to indicate a statistically significant difference.

Results

Changes of the gastric mucosal pH. The gastric mucosal pH values were not significantly different between 2 of the 3 groups prior to treatment (baselines, each at P>0.05). The gastric mucosal pH of group A did not change 6, 12, 24 and 48 h after treatment with drugs compared with the baseline (all at P>0.05), while the gastric mucosal pH in groups B and C were statistically higher at the time points of 6, 12, 24 and 48 h after treatment with drugs compared with the respective baselines (all at P<0.05). After treatment with drugs, the gastric mucosal pH of group C at the time points of 6, 12, 24 and 48 h after treatment were significantly higher than those of group A and group B at these same time points after treatment, while there were statistical differences between groups A and B at the 6, 12, 24 and 48 h time points after treatment (all P<0.05). The results are shown in Table I.

Hemodynamic changes. Hemodynamic indicators of the patients prior to treatment were not significantly different between 2 of the 3 groups (all at P>0.05). Compared with the baseline values, the MAP and cardiac index (CI) of each group after treatment were significantly increased. Following treatment, the PAWP and the CVP of groups B and C significantly increased (all at P<0.05), albeit the two parameters of group A changed only insignificantly. After medication, the heart rate of group A (treated with dopamine) significantly increased (P<0.05) while the heart rate of the other 2 groups increased insignificantly. The results are shown in Table II.

Discussion

Impact of vasoactive drugs on the hemodynamics. The results of this study showed that the vasoactive drugs can raise blood pressure and oxygen delivery levels. In septic shock patients, cardiac dysfunction at varying degrees affected myocardial contractility, reduced CO and resulted in decreased blood pressure (7-9). Vasoactive drugs can increase CO and blood pressure because they cause the contraction of blood vessels (10). Norepinephrine mainly affects α-receptors, increases the cardiac after load, but it shows weak cardiac effects of β-receptor (11-13). The patients in group C were treated with norepinephrine and dobutamine, the MAP, CI, and other hemodynamic parameters were increased and cardiac function significantly improved. The effect of β-adrenergic receptors by dobutamine resulted in the expansion of blood vessels and caused lower blood pressure (14-16). Therefore, blood pressure can be increased and heart function improved in patients with septic shock and hypotension if they are treated with dobutamine at low dose and norepinephrine at normal dose.

Effects of vasoactive drugs on gastric pH. The ideal vasoactive drugs are those that can rapidly raise blood pressure, improve organ perfusion, and increase gastric mucosal pH.

The choice of vasoactive drugs remains the focus of academic debate. Currently, norepinephrine plus dobutamine has become the first medication choice for treatment of septic shock, they can improve blood perfusion of the whole body, especially the blood perfusion of internal organs (17,18). When the shock begins, the use of vasoactive drugs must be taken into consideration to maintain MAP at 70-80 mmHg if a fluid resuscitation cannot maintain the blood pressure. As a β-adrenergic receptor agonist, dobutamine can enhance the myocardial contractility, increase the CO, reduce the peripheral vascular resistance, and improve splanchnic blood perfusion (19-21), in particular, can improve tissue oxygenation and play an antishock effect by maintaining or increasing the level of oxygen delivery (DO_2) or oxygen uptake of tissues. The possible reason for norepinephrine playing a role in the increase of the splanchnic blood delivery and gastric mucosal pH of patients with septic shock is that the positive

Table I. Gastric mucosal pH of 3 groups before (baseline) and after medication (mean ± SD).

Groups	Baseline	Time points after treatment			
		6 h	12 h	24 h	48 h
A	7.21±0.21	7.23±0.13	7.24±0.21	7.25±0.22	7.25±0.03
B	7.20±0.25	7.27±0.17[a]	7.27±0.25[a]	7.27±0.02[a]	7.28±0.03[a]
C	7.20±0.23	7.37±0.21[a,b]	7.37±0.21[a,b]	7.37±0.24[a,b]	7.38±0.02[a,b]

[a]At P<0.05 compared with the baseline in the same group. [b]At P<0.05 compared with groups A and B at the same time point after treatment. SD, standard deviation.

Table II. Hemodynamic indicators before (baseline) and 6 h after medication (mean ± SD).

Groups	MPA, mmHg	HR, times/min	PAWP, mmHg	CVP, mmHg	CI, l/min
Baseline	61±8.1	116±23.6	10.0±2.2	7.0±2.3	4.0±0.7
A	76±4.2[a]	136±23.5[a]	11.4±2.1	8.0±2.7	5.4±0.8[a]
B	75±4.9[a]	116±16.2	14.0±1.8[a]	15.0±2.8[a]	4.8±1.1[a]
C	75±5.0[a]	118±21.3	14.0±1.6[a]	14.8±3.0[a]	5.5±1.1[a]

[a]At P<0.05 compared with the baseline. MPA, mean arterial pressure; HR, hazard ratio; PAWP, pulmonary capillary wedge pressure; CVP, central venous pressure; CI, cardiac index.

inotropic effect of β_2-receptor of norepinephrine caused an increase of CI, DO_2 but did not change the splanchnic blood distribution. Compared with the use of norepinephrine alone, the use of norepinephrine and dobutamine in combination can increase CI and gastric mucosal pH significantly (P<0.05). Investigators considered that this joint effect of norepinephrine and dobutamine is, based on the increase of CI followed by the improvement of the splanchnic blood perfusion, but also based on the improvement of blood circulation in stomach due to the redistribution of the blood flow in mucous layer of the stomach wall (22). The results of the present study showed that the gastric mucosal pH was significantly increased 6 h after administration of norepinephrine and dobutamine in combination (group C), but the pH after treatment with dopamine alone did not clearly change (group A). The reason may be that the imbalanced supply and demand of local oxygen, or the shortage of blood supply caused by redistribution and short circuit of blood flow in gastrointestinal mucous membrane. In this study, the gastric mucosal pH of the norepinephrine-treated patients (group B) increased to a certain extent but was insignificantly different from that of patients treated with norepinephrine plus dobutamine (group C). The reason for this was that the strong vasoconstriction effects of norepinephrine may still affect the visceral blood perfusion (23-25).

The results suggested that the use of norepinephrine and dobutamine in combination can more effectively improve the splanchnic perfusion in comparison to the use of dopamine or norepinephrine alone, and the co-effect of norepinephrine and dobutamine may be related to the changes of intestinal blood flow distribution by dobutamine.

Significance of monitoring the pH of the gastric mucosa. The gastric mucosal pH is a sensitive indicator reflecting the ischemia and hypoxia of gastric mucosa, suggesting that successful resuscitation concealed the risk of visceral ischemia, especially the risk of gastrointestinal ischemia (26,27). The normal pH value is 7.38±0.03, while reduced gastric mucosal pH indicated the presence of hypoxia and hypoperfusion in intestinal tissue. At 2-3 days prior to the dysfunction of multiple organs, visceral hypoperfusion was evident (28). The oxygenation obstacles appeared initially in the gastrointestinal mucosa and the gastric mucosa recovered later. Sometimes the pH of gastric mucosa is at a low value after the systemic monitoring indicators have returned to normal. The low value of the gastric mucosal pH is a recessive shock (29). At this point, the patient should be treated continually for resuscitation until the gastric mucosal pH is corrected. Therefore, the continuous dynamic monitoring of the pH is important for ischemia of the gastrointestinal tract. The key points to shock resuscitation are the improvement of tissue hypoperfusion and the reversing of tissue ischemia and hypoxia, and the measurements for these purposes are the use of vasoactive drugs and the addition of blood volume vasoactive drugs have different effects on gastric mucosal pH (30). Although lactic acid is a systemic index for adequacy of tissue perfusion, the blood flow is not evenly distributed into all types of tissue beds. Local tissues are subjected to hypoperfusion even though the overall perfusion index is normal. The gastric mucosal pH is a sensitive indicator for monitoring the blood perfusion of local tissues of patients with septic shock (31). Gastrointestinal ischemia can cause increased gastrointestinal permeability, the transfer of bacteria and toxins through the intestinal wall, the release of

large amounts of inflammatory mediators, and lead to sepsis, which is the initiating factor for multiple organ dysfunction syndromes. It has been found in recent years that gastric mucosal pH can be used as an important indicator to test the effective recovery of the shock resuscitation and as a warning for the complications after resuscitation (32). Thus, the present findings have shown that the use of vasoactive drugs cannot correct the pH of the gastric mucosa even if the arterial blood pressure and systemic hemodynamics have been corrected and the results indicated that the simple increase of the arterial blood pressure in septic shock is clearly insufficient, therefore, attention should be paid to splanchnic perfusion.

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