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Comparison of norepinephrine, dopamine and dobutamine combined with enteral nutrition in the treatment of elderly patients harboring sepsis

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Abstract: The present study was performed in order to investigate the safety and efficacy of different vasoactive drugs combined with enteral nutrition in terms of treating elderly patients with sepsis. A total of 75 elderly patients with sepsis treated with enteral nutrition in our hospital were randomly divided into three groups: group A (n = 25), group B (n = 25) and group C (n = 25). The three groups were treated with dopamine, dobutamine and norepinephrine respectively. One week after treatment, the therapeutic effects of the three groups were compared, the vascular elastic indexes, hemodynamic indexes and levels of inflammatory factors of the three groups were measured. After treatment, the clinical effective rate of group C was evidently higher than that of group A and group B. The vascular elasticity coefficient and stiffness coefficient in group C were significantly lower than those in group A and group B, and the arterial compliance in group C was significantly higher than that in group A and group B ($P < 0.05$). The levels of MAP and PVRI in group C were significantly higher than those in group A and B, and the levels of CI, CVP and HR in group C were significantly lower than those in group A and group B ($P < 0.05$). Norepinephrine elicited greater effects in terms of improving hemodynamic indexes, vascular elasticity and reducing the level of inflammatory factors compared with dopamine and dobutamine in elderly patients harboring sepsis.

Keywords: Sepsis, senility, vasoactive drugs, enteral nutrition.

INTRODUCTION

Sepsis is a series of infectious shock caused by the response of a host with life-threatening organ dysfunction to infection. It has been a major health issue and burden on our society, with more than 60% of sepsis occurring in elderly patients aged 65 and older(Stolk *et al.*, 2016; Li and Sun, 2019). Factors that increase the risk of sepsis in the elderly may include congestive heart failure, chronic obstructive pulmonary disease, malignant tumors, diabetes, and chronic liver failure. Long-term diabetes can lead to delayed phagocytosis, decreased clearance of yeast and bacteria by neutrophils, and chronic liver failure that leads to the formation of complement factors and the disturbance of cellular immune proliferation. Physiological changes associated with chronic obstructive pulmonary disease, including impaired mucociliary clearance, alveolar macrophage dysfunction and cough inhibition mechanism, which significantly increase the risk of lower respiratory tract infection in the elderly. Weakness is regarded as one of the common clinical syndromes in the elderly, which is related to a series of medical problems caused by the declined ability of daily activities. Therefore, the increased traumatic falls and injuries lead to hospitalization and the elderly are easily exposed to hospital infection. With the increase of aging population in China in recent years, more focus should be laid on the high incidence of sepsis in the elderly population(Seymour and Rosengart, 2015; Sauer *et al.*, 2016). According to sepsis treatment guidelines, dopamine, dobutamine and norepinephrine can be considered as first-line drugs for the treatment of sepsis. In our study, there involved 75 elderly septic patients treated with enteral nutrition in our hospital, with an attempt to investigate and compare the safety and efficacy of the three above mentioned vasoactive drugs.

MATERIALS AND METHODS

General information

In this study, there involved a total of 75 elderly patients with sepsis treated with enteral nutrition in our hospital from September 2017 to March 2018. The study protocol was approved by the Ethics Committee of Wuhan No.6 Hospital, and written informed consent was obtained from the patients.

Inclusion criteria

1) patients diagnosed with sepsis based on the diagnostic criteria;

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2) aged 60-75 years old, regardless of gender;
3) enteral nutrition was performed after admission;
4) complete clinical data;
5) available follow-up.

Exclusion criteria

1) patients who failed to receive enteral nutrition;
2) patients with malignant tumor;
3) patients with severe abnormality of liver and kidney function;
4) patients with immune system diseases;
5) patients with mental diseases;
6) incomplete clinical data.

Research methods

Grouping of subjects

A total of 75 elderly patients with sepsis were randomly divided into three groups: group A (n=25), group B (n= 25) and group C (n=25). The three groups were respectively treated with dopamine, dobutamine and norepinephrine.

Treatment

All patients were treated with intravenous fluid replacement, central venous catheterization and rapid infusion of 40mL/kg fluid. When the third 20mL/kg fluid was injected, the patients in groups A, B and C received small amount of dopamine (group A, the initial dose of dopamine was 7.0μg/kg/min), dobutamine (group B) and norepinephrine (group C). If the treatment target was not achieved, the doses could be increased by 2.5μg/kg/min per 20min, up to a maximum of 20.0μg/kg/min; the dosage of dobutamine (Shandong Fangming Pharmaceutical Group Co., Ltd., H20053297) in group B was 2-20μg/kg/min for 5 days; the initial dose of norepinephrine in group C was 0.1μg/kg/min, and the doses could be increased by 0.1μg/kg/min per 20min, up to a maximum of 0.3μg/kg/min to reach the therapy effect. The other treatments of the three groups were the same, all of them were treated with antibiotics, mechanical ventilation and so on.

Observation indicators

1) The baseline data of gender, age and location of primary infection were collected and compared among the three groups. 2) In order to evaluate the therapeutic effect of the patients in three groups, the criteria were as follows: significantly effective represented complete remission of clinical symptoms, effective control of infection site, and recovery of laboratory indexes to normal level; effective represented the relieved clinical symptoms, the normal level of laboratory indicators, the infection site was not completely controlled; ineffective represented the unimproved or worse clinical symptoms. Total efficiency = (significantly effective + effective) / total × 100%. 3) The pressure strain elastic coefficient,

Table 1: Comparison of baseline data of three groups before treatment (n = 25)

Group	Gender (male/female)	Age (year)	Site of primary infection (n)			
			Lung	Biliary tract	Urinary system	Blood flow
Group A	15/10	69.16±8.24	10	5	7	3
Group B	16/9	70.03±8.59	9	5	8	3
Group C	16/9	69.86±8.10	10	4	8	3
χ^2/F value	0.440	0.866	0.025			
P value	>0.05	>0.05	>0.05			

Table 2: Evaluation of therapeutic effect of three groups of subjects (n, %) (n = 25)

Group	Significantly effective (n)	Effective (n)	Ineffective (n)	Effective rate(%)
Group A	7	13	5	80.00
Group B	8	12	5	80.00
Group C	15	8	2	92.00[ab]
χ^2 value	-	-	-	9.630
P value	-	-	-	<0.05

Table 3: Comparison of vascular elasticity indexes in three groups after treatment ($\overline{x}$ ±s, n = 25)

Group	Pressure strain elastic coefficient (kPa)	stiffness index	Arterial compliance (mm^2/kPa)
Group A	132.44±11.53	7.74±0.73	0.56±0.08
Group B	129.81±12.70	7.50±0.67	0.59±0.10
Group C	110.54±11.91 [ab]	6.69±0.65 [ab]	0.71±0.13 [ab]
F value	8.971	4.821	5.520
P value	<0.05	<0.05	<0.05

Table 4: Comparison of hemodynamic indexes among the three groups after treatment ($\bar{x}$ ±s, n = 25)

Group	MAP (mm Hg)	PVRI (dyn·s·cm^2 /m^5)	CI (L/min)	CVP (mm Hg)	HR(/min)
Group A	82.36±12.33	98.90±10.22	5.62±0.94	10.20±1.20	108.63±8.14
Group B	84.09±10.81	102.47±9.15	5.57±0.90	9.97±1.13	107.11±9.60
Group C	93.17±13.64 [ab]	122.48±9.88 [ab]	5.09±0.82 [ab]	8.15±0.86 [ab]	97.89±9.55 [ab]
F value	10.639	12.622	5.471	6.172	6.833
P value	<0.05	<0.05	<0.05	<0.05	<0.05

Table 5: Comparison of inflammatory cytokines in three groups after treatment ($\bar{x}$ ±s, n = 25)

Group	PCT (ng/L)	PAF (ng/L)	TNF-α (ng/L)
Group A	2.13±0.39	1018.47±95.85	38.44±4.12
Group B	2.08±0.41	1021.30±99.74	38.40±4.08
Group C	1.20±0.21 [ab]	852.76±63.19 [ab]	31.79±3.65 [ab]
F value	6.182	10.260	7.155
P value	<0.05	<0.05	<0.05

Note: compared with group A, [a]P < 0.05; compared with group B, [b]P < 0.05

Table 6: Comparison of complications among the three groups after treatment (n, %) (n = 25)

Group	Hyperglycemia	Abdominal distension and diarrhea	superinfection	Stress ulcer
Group A	1(4.00)	2(8.00)	1(4.00)	0(0.00)
Group B	0(0.00)	2(8.00)	1(4.00)	1(4.00)
Group C	1(4.00)	1(4.00)	0(0.00)	0(0.00)
χ^2 value	0.336	0.508	0.061	0.809
P value	>0.05	>0.05	>0.05	>0.05

stiffness index and arterial compliance of the three groups were measured by color Doppler ultrasonography. 4) The noninvasive mean arterial pressure (MAP), peripheral vascular resistance index (PVRI), cardiac output (CI) and central venous pressure (CVP), heart rate (HR) and other hemodynamic indexes were compared and measured by digital non-invasive hemodynamic monitoring system. 5) The level of inflammatory factors such as procalcitonin (PCT), platelet activating factor (PAF) and tumor necrosis factor-α (TNF- α) were measured by enzyme-linked immunosorbent assay (ELISA) in three groups. 6) The complications such as hyperglycemia, abdominal distension, diarrhea, superinfection and stress ulcer were recorded in the three groups after treatment.

STATISTICAL ANALYSIS

All data of our study were processed by SPSS20.0 statistical analysis software (IBM Company of USA). Measurement data is expressed as mean ± standard deviation. Comparison between groups was performed using one-way analysis of variance or repeated analysis of variance, and pairwise comparison between groups was performed using LSD-t test. The counting data were expressed by percentage (%), and χ 2 analysis was used to compare the data among different groups, A P < 0.05 represented significant statistical difference.

RESULTS

Comparison of baseline data of three groups before treatment

The results showed that there was no significant difference in age, sex and primary infection site among the three groups. (P>0.05), as shown in table 1.

Evaluation of therapeutic effect of three groups

After treatment, the clinical effective rate of group C was 92.00%, which was significantly higher than that of group A and group B with significant statistical difference (P < 0.05). The clinical effective rate of the patients in group A and group B was 80.00%, but there was no significant difference between the two groups (P>0.05), as shown in table 2.

Comparison of vascular elasticity among the three groups after treatment

The pressure strain elastic coefficient and stiffness index in group C were significantly lower than those in group A and group B, and the arterial compliance in group C was significantly higher than that in group A and group B (P< 0.05). No significant difference was observed in vascular elasticity between group A and group B (P>0.05), as shown in table 3.

Comparison of hemodynamic indexes among the three groups after treatment

MAP and PVRI in group C were significantly higher than those in group A and B, while CI, CVP and HR in group C were significantly lower than those in group A and group B ($P<0.05$). There was no significant difference in hemodynamic indexes between group A and group B ($P> 0.05$), as shown in table 4.

Comparison of inflammatory cytokines in three groups after treatment

The levels of PCT, PAF and TNF- α in group C were significantly lower than those in group A and group B, with significant statistically difference ($P<0.05$). There was no significant difference in the level of inflammatory cytokines between group A and group B ($P>0.05$), as laid out in table 5.

Comparison of complications among three groups of subjects after treatment

After treatment, there was no significant difference in the incidence of complications including hyperglycemia, abdominal distension, diarrhea, superinfection and stress ulcer among the three groups ($P>0.05$), as laid out in table 6.

DISCUSSION

Sepsis is one of the most common death cause of intensive care units and with a trend towards gradual increase with the passage of time, which mostly occurs among elderly patients. It has been acknowledged that immune function decreases with age, also known as immune aging, which increases the risk of infection in the elderly. It also increases the risk of older persons being infected with more severe and longer-term processes. Sepsis is characterized by the activation of inflammation leading to the expansion of veins and arteries, resulting in a reduction in systemic vascular resistance and systolic pressure. The decrease of blood pressure and the low perfusion of important organs lead to multiple organ failure, resulting in an increase in mortality from septic shock. Therefore, one of the early goals of resuscitation in patients with septic shock is to restore adequate organ perfusion (Ait-Oufella *et al.*, 2015; Kandasamy *et al.*, 2016; Zampieri *et al.*, 2019).

Dopamine, the precursor of norepinephrine, acts on dopaminergic receptors, b-adrenergic receptors and a-adrenergic receptors in a dose-dependent manner(Branco, 2016), which increases mean arterial pressure mainly by increasing cardiac index and systemic vascular resistance to some level (Ventura *et al.*, 2015; Ramaswamy *et al.*, 2016). Dobutamine is a synthetic catecholamine acting on α-1, β-1 and β-2 adrenergic receptors (Sakai *et al.*, 2017). It is widely used all over the world and is listed in early goal-oriented therapy (Bhattacharjee *et al.*, 2017). Since the introduction in early goal-oriented therapy, dobutamine has been considered to be an important component, especially in patients with infective myocardial dysfunction (Meng *et al.*, 2016). Currently, the survival sepsis campaign guidelines recommend the use of dobutamine in the presence of myocardial dysfunction, which is indicated by increased cardiac filling pressure and decreased cardiac output or persistent low perfusion. Although vascular content and mean arterial pressure are sufficient, it is doubtful whether dobutamine improves the mortality of sepsis and septic shock. Norepinephrine is an effective α-adrenergic receptor, which has activity on B1 adrenergic receptor (Seyedi *et al.*, 1997). According to some observational studies, the use of dopamine in septic shock may increase mortality. However, a recent observational study of patients with community-acquired sepsis reported that norepinephrine-treated patients had a poor prognosis. Therefore, debate exists regarding the selection of safer as well as more effective vasoactive drug in the treatment of sepsis.

In the current study, the clinical effective rate of group C was significantly higher than that of group A and group B after treatment. The levels of vascular elasticity index (pressure strain elastic coefficient, stiffness index, arterial compliance), hemodynamic indexes (MAP, PVRI, CI, CVP, HR) and inflammatory factors (PCT, PAF, TNF- α) were significantly better than those of Group A and group B ($P<0.05$). The aggregated results indicated that norepinephrine had a better therapeutic effect than dopamine and dobutamine. The abovementioned results may attribute to the following reasons(Gordon *et al.*, 2016; Hamzaoui *et al.*, 2017). First, norepinephrine elicits greater effect as vasopressors than dopamine and is more effective in reversing hypotension in septic shock. In patients with sepsis, norepinephrine increases blood pressure, cardiac output, kidney, visceral, cerebral and microvascular blood flow, while minimally increasing heart rate, which achieves superior effects on hemodynamic levels to dopamine in maintaining organ perfusion. Second, dopamine and dobutamine may increase the risk of secondary infection. Dopamine inhibits the function of anterior pituitary gland and leads to the decrease of the secretion of prolactin, growth hormone and thyroid stimulating hormone. Prolactin and growth hormone have the characteristics of immune evaluation. It is reported that dopamine and dobutamine can also inhibit lymphocyte proliferation, immunoglobulin synthesis, cytokine production and promote lymphocyte apoptosis. In septic shock model in mice. dopamine can reduce splenocyte proliferation and IL-2 release, and increase mortality compared with placebo. As a result, dopamine may increase the risk of infection.

CONCLUSION

To sum up, norepinephrine elicits greater beneficial effects than dopamine and dobutamine in terms of improving hemodynamic indexes, vascular elasticity and reducing the level of inflammatory factors in elderly patients with sepsis. Therefore, norepinephrine may be a safer and more efficient drug in treating patients with sepsis.

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