Original Article
The effects of vasoactive drugs combined with volume management on the myocardial consumption of oxygen and pulmonary function in patients with severe burns

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Abstract: Background: This study aimed to investigate the effect of dopamine or phenylephrine combined with restrictive liquid on the blood pressure, myocardial consumption of oxygen, and pulmonary function in patients with severe burns. Methods: Sixty patients with severe burns, scheduled for skin grafting surgery under general anesthesia, were divided into three groups (n = 20 each). The patients in group A received dopamine combined with restricted liquid. The patients in group B received phenylephrine combined with restricted liquid. Those in group C received no vasoactive drugs and had liberal liquid. Systolic blood pressure (SBP), heart rate (HR), heart rate-systolic blood pressure product (RPP), oxygenation index (OI), airway peak pressure (Ppeak), lung compliance (Cdyn), central venous pressure (CVP), liquid input volume, and urine output during the surgical skin grafting were compared among the three groups. Results: The HR and RPP of the patients in group B were significantly lower than they were in groups A and C ($P<0.05$). The CVP and liquid input volume of the patients in groups A and B were significantly lower than they were in group C ($P<0.05$). There were no significant differences in the SBP or the urine output among the three groups ($P>0.05$). The OI and Cdyn of the patients in groups A and B were higher than they were in group C, but the Ppeak was lower ($P<0.05$). Conclusions: The application of dopamine or phenylephrine combined with restrictive liquid in severe burn surgery can maintain stable circulation without reducing the urine output, significantly improve OI and Cdyn, and reduce cardiopulmonary complications. The phenylephrine can also reduce the myocardial consumption of oxygen.

Keywords: Dopamine, phenylephrine, liquids, intravenous, burns, lung, oxygen consumption

Introduction

Patients with severe burns often suffer from multiple organ dysfunction. Although they have been treated actively, the cardiopulmonary and other important organ functions are still relatively fragile. Severe burn injuries can significantly affect cardiovascular function for up to 3 years [1]. Pulmonary edema often occurs after severe burns and can lead to acute lung injury, acute respiratory distress syndrome (ARDS) [2], and even multiple organ failure. The mortality of patients with ARDS is extremely high, and deaths are mostly due to multiple organ failure [3, 4]. Restrictive fluid resuscitation provides good oxygenation in ARDS [5]. It has been widely used in clinics in recent years. Restrictive liquid can not only ensure tissue perfusion and oxygen supply, but it can also reduce interstitial lung water and contribute to oxygen diffusion from the alveoli to the pulmonary capillaries. However, there are still risks of circulatory instability with restrictive fluid resuscitation. Vasoactive drugs may play a positive role in critically ill patients. The aim of this study was to investigate the effects of vasoactive drugs combined with restrictive liquid on the blood pressure, myocardial oxygen consumption, and pulmonary function in patients undergoing severe burn surgery.

Materials and methods

Participants

This study was approved by the hospital ethics committee, and informed written consents were provided by the patients or their relatives. A retrospective analysis was conducted, which included 60 patients with severe burns at the

First Hospital of Shijiazhuang for surgery under general anesthesia from March 2016 to December 2018. Among them, 44 were male and 16 were female. The patients were aged 23~58 years old. All the patients were in a physical status of II or III according to the American Society of Anesthesiologists (ASA) guidelines. The patients were assigned into three groups, with 20 patients in each group and were treated with different vasoactive drugs during their operations. The patients in group A received dopamine combined with restricted liquid. The patients in group B received phenylephrine combined with restricted liquid. The patients in group C received no vasoactive drugs and had liberal liquid.

Inclusion criteria: (1) The total area of the burns was more than 30%, or the area of the third-degree burns was more than 10%. (2) The patients were conscious and had passed the shock stage. (3) The cardiac function was good before the operation, and the level of brain natriuretic peptide (BNP) was lower than 400 pg/mL. (4) The oxygenation index before the operation was higher than 300 mmHg and the patients showed no obvious dyspnea and mechanical ventilation was not required. (5) The kidney function was good, with a 24-hour urine output greater than 400 mL. (6) The pre-operative albumin level was higher than 25 g/L. Exclusion criteria: (1) The total area of the burns was less than 30%, or the area of the third-degree burns was less than 10%; (2) Patients severe acid and alkali chemical burns; (3) Patients with consciousness disorders; (4) Patients needing ventilator-assisted breathing; (5) Patients with diabetic ketoacidosis; (6) Patients with severe heart, lung, liver, or kidney dysfunction.

Anesthesia methods

All patients were deprived of food for 8 h and water for 2 h. After entering the operating room, the patients were given sodium lactate Ringer's solution through open venous access. The electrocardiogram and pulse oxygen saturation were monitored routinely. Radial artery puncture or dorsal pedal artery puncture catheterization was done under local anesthesia for monitoring the invasive arterial blood pressure. Five minutes before the anesthesia began, the patients in group A were given dopamine at a rate of 5 ug/kg/min, and those in group B were given phenylephrine at a rate of 0.5 ug/kg/min. And then, the dosage was adjusted until the operation ended to maintain a stable blood pressure. However, there were no vasoactive drugs in group C. The restrictive liquid strategy was applied in groups A and B, and the sodium lactate Ringer solution was maintained at 6 mL/kg/h. A liberal fluids strategy was adopted in group C. Blood was transfused if necessary, based on blood loss. The anesthesia induction was done slowly using midazolam (0.04 mg/kg), etomidate (0.3 mg/kg), cisatracurium (0.2 mg/kg), and fentanyl (4 μg/kg), followed by tracheal intubation, and then mechanical ventilation was used. The oxygen flow rate was 2 L/min, the tidal volume was 7 mL/Kg, the respiratory rate was 13-15 rates/min, and the pressure of the end-tidal carbon dioxide was maintained at 35-45 mmHg. The central vein was punctured and catheterized to the monitor central venous pressure. The anesthesia was maintained by the inhalation of 1.0% sevoflurane, and the intravenous infusion of propofol at 3-4 mg/kg/h and remifentanil 0.05-0.1 μg/kg/min. Fentanyl 2 μg/Kg was added during the escharectomy and skin removal, and cisatracurium 0.06 mg/kg was added every 30-40 min during the operation. During the operation, the blood pressure and heart rate were kept stable, and the fluctuation range was not more than 20% of the baseline value. When the blood pressure decreased, the volume was supplemented actively to maintain the central venous pressure at 6-12 cmH_2O. If necessary, a bolus intravenous injection of phenylephrine at a low dose of 20-40 μg was applied. When the operation ended, the inhalation of anesthetics was stopped. The tracheal tube was removed after the patient was fully revived.

Observation indices

The systolic blood pressure and heart rates were recorded during the skin grafting. The heart rate and systolic blood pressure product can be used as an index to evaluate myocardial oxygen consumption during anesthesia. It is best to keep the index below 12,000 during an operation. At the same time, 1 mL of arterial blood was collected for a blood gas analysis. The PaO_2 was recorded, and the oxygenation index (OI, OI = PaO_2/FiO_2) was calculated. The respiratory parameters, tidal volumes (VT),

Table 1. Patient demographics ($n = 20$, $x \pm s$)

Gp	ASA II/III	Age (years)	Sex (male/female)	Operating time (min)	bleeding (mL)	burn area (%)
A	7/13	46.14±8.25	16/4	171.55±30.63	854.25±64.72	47.38±15.71
B	6/14	45.37±7.62	15/5	168.50±27.04	876.31±71.25	53.46±16.34
C	8/12	47.36±6.54	14/6	157.68±31.52	861.27±86.54	51.26±18.32
X^2/F	0.114	0.402	0.143	0.332	276.251	0.451
P	0.736	0.690	0.705	0.741	0.653	0.662

ASA: American Society of Anesthesiologists guidelines.

Table 2. Comparison of the circulatory indexes in the three groups ($n = 20$, $x \pm s$)

Gp	SBP (mmHg)	HR (beats/min)	RPP	CVP (cmH$_2$O)	Liquid (mL)	Urine Output (mL)
A	110.800±4.962	79.700±4.877	8823.500±542.591	6.700±0.675	1350.000±88.192	493.000±33.350
B	107.400±7.306	71.800±4.894	7711.000±736.278	7.100±0.728	1283.000±84.990	490.000±83.133
C	105.300±6.056	78.6±4.300	8279.300±688.160	10.000±0.943	2625.000±162.019	476.000±30.258
F	2.015	8.293	7.087	51.512	415.877	0.276
P	0.153	0.002	0.003	0.000	0.000	0.761

SBP: systolic blood pressure; HR: heart rate; RPP: heart rate-systolic blood pressure product; CVP: central venous pressure.

respiratory frequencies (f, rates/min), and peak airway pressures (Ppeak) were recorded, and the pulmonary compliance (Cdyn = VT/Ppeak - PEEP) was calculated. The fluid infusions and urine outputs after the operations were compared between the two groups.

Statistical analysis

The measurement data were expressed as the mean ± SD. Analysis of variance (ANOVA) was used to compare means of several groups. The means of the two groups were compared using *t*-tests. The count data were presented as n (%), and the differences in rates were evaluated using chi-squared tests. The data were analyzed using SPSS software (version 23.0), and $P<0.05$ was considered statistically significant.

Results

The sixty patients enrolled in this study were divided into groups A, B and C. The patients in group A received dopamine combined with restricted liquids. Those in group B received phenylephrine combined with the restricted liquid strategy. The patients in group C received liberal fluid management without vasoactive drugs. The demographics of the enrolled patients are summarized in **Table 1**. There were no significant differences in ASA grade, age, sex, operating time and bleeding volume, or burn area among the three groups (P = 0.736,

0.690, 0.705, 0.741, 0.653, and 0.662, respectively).

The circulatory indexes of the patients are summarized in **Table 2**. Compared with group C, the liquid volumes of the patients in groups A and B were significantly lower, indicating that the patients were given strict restrictive liquid management. Meanwhile, the restrictive liquid management did not reduce the urine output of the patients in group A and B. The HR and RPP of the patients in group B were significantly lower than they were in groups A and C ($P<0.05$). The CVP levels of the patients in groups A and B were significantly lower than they were in group C ($P<0.05$). As for SBP, there were no significant differences among the three groups ($P>0.05$) (**Table 2**).

The respiratory indexes of the subjects are summarized in **Table 3**. The OI and Cdyn of the patients in groups A and B were significantly higher than they were in group C (P<0.05), and the Ppeak was significantly lower than it was in group C (P<0.05), indicating that the respiratory conditions of the patients were improved in groups A and B. However, there were no significant differences in terms of V$_T$, f, or PEEP among the three groups ($P>0.05$) (**Table 3**).

Discussion

During the burn shock stage, due to the increase in pulmonary vascular permeability and

Table 3. Comparison of the respiratory parameters in the three groups (n = 20, $\bar{x} \pm s$)

Groups	OI (mmHg)	V_T (mL)	f (rates/min)	Ppeak (cmH$_2$O)	PEEP (cmH$_2$O)	Cdyn (mL/cmH$_2$O)
A	399.200±39.986	466.200±6.015	14.600±0.516	17.100±0.738	2.300±0.483	31.557±1.530
B	393.200±37.499	467.900±6.790	14.100±0.738	16.400±0.966	2.300±0.675	33.371±2.731
C	312.400±38.549	468.600±9.407	14.100±0.876	20.400±1.647	2.200±0.422	25.894±2.205
F	15.697	0.268	1.585	32.682	0.115	31.122
P	0.000	0.767	0.224	0.000	0.891	0.000

Cdyn: lung compliance; Ppeak: airway peak pressure; OI: oxygenation index.

the decrease in plasma colloid osmotic pressure, adequate fluid resuscitation often leads to an accumulation of fluid in the pulmonary interstitial space, and varying degrees of pulmonary edema occur in burn patients during the retroabsorption stage. Restrictive liquid is an innovative fluid management strategy for patients with severe burns. Appropriate restrictive liquid and the reasonable control of fluid infusion speed and total volume not only ensure the effect of fluid resuscitation, but they also protect the functions of tissues and organs from damage. Clinical practice has shown that the restrictive liquid strategy can help balance body fluid distribution, alleviate pulmonary edema, and improve patient prognosis [6]. The restrictive liquid strategy was applied in this study. The central venous pressures of the patients in groups A and B were maintained at a low level, and the liquid volume was significantly lower than it was in group C. Low central venous pressure technology can improve the prognoses of critically ill patients [7]. Another important feature of large area burns is the low resistance of the peripheral blood vessels, vasodilation, and capillary leakage. Therefore, vasoactive drugs combined with restrictive liquids are better for the pathophysiological characteristics of severe burns.

Dopamine and phenylephrine are commonly-used vasoactive drugs in clinics to maintain the stability of the blood pressure and the heart rate. The characteristics of the two drugs are different. Although dopamine is a controversial drug, and its anti-shock and renal protective effects are questioned, dopamine is still widely used clinically [8]. Traditionally, dopamine is considered a dose-dependent drug. Different doses act on different receptors and exert different clinical effects. When it is injected at 0.5-2 μg/kg/min, the dopamine receptors are mainly activated to dilate the renal and mesen-

teric blood vessels and increase the renal blood flow and the glomerular filtration rate. It is also believed that the increase in renal blood flow caused by a low dose of dopamine is mainly attributed to its positive inotropic effect, not the direct dilation of the renal blood vessels. The increase in urine output caused by dopamine is due to its direct renal tubular natriuretic and diuretic effects. When the dose increased to 2-5 μg/kg/min, dopamine increases myocardial contractility through beta excitation. The alpha receptor is activated when the dose is higher than 5 μg/kg. min. When dopamine is less than 5 μg/kg/min, the vein may contract preferentially, and the cardiac output may be improved. There is a clear overlap between the above doses of dopamine and the activation of the receptor, and there is no obvious limit. While dopamine maintains circulation stability, the positive muscle tone and frequency of dopamine will increase myocardial oxygen consumption, leading to a high risk of tachycardia, arrhythmia and cardiac events [9, 10].

Due to the impairment of cardiac function, stress responses, inflammatory responses, pain stimulation, and insufficient capacity, patients with severe burns often have a heart rate that is too fast, increasing their myocardial oxygen consumption and easily inducing tachyarrhythmia. The heart rate-systolic pressure product is an index for evaluating myocardial oxygen consumption [11]. In this study, the heart rate, myocardial oxygen consumption, and heart rate-systolic blood pressure product in one group were significantly lower than they were in the other two groups. The mechanisms of action of phenylephrine and dopamine are different. Phenylephrine is a pure alpha-receptor stimulant, and it mainly activates the alpha-1 receptor of vascular smooth muscle. The clinical dose of phenylephrine can constrict small arteries and venules, and increase blood pres-

sure. And the contraction of venous vessels can temporarily increase venous reflux and improve cardiac output [12]. Baroreceptor excitation leads to slow reflex heart rate, prolonged diastolic period, and increased myocardial contractility. Phenylephrine can stabilize circulation when combined with restrictive liquids. It not only maintains blood pressure, it also slows down the heart rate [13], which is beneficial to burn patients. Therefore, it can increase cardiac output and reduce myocardial oxygen consumption, so it is better than dopamine.

Within the dose range used in this study, there were no significant differences in the systolic blood pressure or urine output among the three groups. There were no cardiovascular adverse events in the dopamine group. During the process of maintaining the intraoperative blood pressure, there was no decrease in the urine output in the groups due to the restriction of liquid volume. Low-dose liquid did not reduce the renal blood flow, and the renal perfusion was adequate. Therefore it can increase the renal blood flow [14]. It is suggested that the volume of liquid should be reduced by 40% or 6-7 mL/kg/h in 3 h. The incidence of pulmonary edema, pneumonia, and respiratory failure may increase within 3 days after the hypervolemic liquid administration, but too little volume is significantly associated with acute kidney injury [15].

Compared with the massive liquid group, the oxygenation index and the lung compliance in the dopamine and groups increased significantly, and the peak airway pressure decreased significantly. Restrictive fluid management can improve lung compliance. Normally, PaO_2/FiO_2 is higher than 400 mmHg. When the gas exchange capacity decreases, such as more lung water, the oxygenation function of the lungs is affected and the oxygenation index decreases. Pulmonary compliance responds to the elastic retractions of the lungs, which reflects the changes in the respiratory cycle during mechanical ventilation. When lung lesions occur, airway resistance increases and lung compliance decreases. It is reported that dopamine can accelerate the absorption of pulmonary edema [16] and improve hypoxemia during one-lung ventilation in thoracic surgery [17]. Dopamine can reduce the release of inflammatory mediators, alleviate pneumonic reaction, and improve lung function [18]. Dopamine mediated protective effects on damage and inflammation in the lungs are most likely mediated via adrenergic receptors [19].

There are still some deficiencies in this study. Due to the limitations of our local conditions, CVP monitoring was carried out, but no high-level monitoring, for example, cardiac output, stroke variance index, etc., was carried out. At present, although there are many controversies about CVP monitoring and its value is considered limited, its dynamic changes still have clinical significance and can provide necessary information [20]. High CVP is always actually pathological.

To sum up, the application of dopamine or phenylephrine combined with restrictive liquid in severe burn surgery can maintain a stable circulation effectively without reducing urine output, can improve the oxygenation index and pulmonary compliance, and can reduce cardiopulmonary complications. It can also reduce myocardial oxygen consumption. This method can reduce cardiopulmonary complications, such as pulmonary edema, heart failure, etc., which can help with the rapid recovery of patients.

Disclosure of conflict of interest

None.

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