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Original Article

Effects of dexmedetomidine combined with sevoflurane for controlled hypotension on the renal function in craniocerebral operation

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Abstract: Objective: To explore the effects of dexmedetomidine combined with sevoflurane for controlled hypotension on the renal function in craniocerebral operation. Methods: A total of 90 patients undergoing craniocerebral operation were analyzed retrospectively, and divided into Group A, Group B, and Group C (each n = 30). Patients in Group A and Group B were given controlled hypotension through infusion of dexmedetomidine by a syringe pump and inhalation of sevoflurane after trauma craniotomy, and the mean arterial pressure (MAP) of Group A and Group B was controlled at 50-55 mmHg and 60-65 mmHg, respectively. In contrast, patients in Group C were not given controlled hypotension. The MAP was recorded at the beginning of blood pressure reduction (T0), 60 min after pressure reduced to target level (T1), and 60 min (T2) and 24 h (T3) after blood pressure reduction stopped. Peripheral venous blood was sampled from patients of each group and their creatinine, blood urea nitrogen, cystatin C, and glomerular filtration rate were compared. Results: There was no significant difference in general clinical data among the three groups. The highest MAP at T1 was seen in Group C, followed by Groups B and A (all $P<0.05$). Group A and Group B showed significantly lower MAP at T1 than that at T0 (both $P<0.05$). At T1, Group A and Group B showed significantly increased creatinine, blood urea nitrogen, and cystatin C levels compared with Group C, and Group A showed significantly higher levels of them than Group B (all $P<0.05$). At T2 and T3, Group A showed significantly higher creatinine, blood urea nitrogen, and cystatin C levels than Group B and Group C (all $P<0.05$). At T0, there was no significant difference among the three groups in glomerular filtration rate ($P>0.05$), at T1, Group A and Group B showed significantly decreased glomerular filtration rate level compared with Group C (both $P<0.05$), and at T2 and T3, Group A showed significantly lower glomerular filtration rate than Group B and Group C ($P<0.05$). Conclusion: Dexmedetomidine combined with sevoflurane is effective in blood pressure reduction in craniocerebral operation. Controlled hypotension to 50-55 mmHg can cause reversible decrease of glomerular filtration function, but 60-65 mmHg is appropriate, so controlled hypotension to 60-65 mmHg is worthy of clinical application.

Keywords: Dexmedetomidine, sevoflurane, craniocerebral operation, renal function

Introduction

Due to high intracranial pressure during neurosurgical procedures, blood will diffuse into the visual operative field after vascular injury, which seriously hinders operation processing [1, 2]. Controlled hypotension reduces intraoperative bleeding by reducing vascular pressure, which improves operation conditions, without compromising the visual operative field [3, 4]. Clinical data reveal that in various surgeries, with controlled hypotension during anesthesia, the mean arterial pressure (MAP) in blood pressure is maintained at 50-60 mmHg, which is safe and tolerable for patients, and the intraoperative blood loss and blood transfusion are significantly decreased [5]. Decreased cerebral perfusion pressure during controlled hypotension does not reduce brain oxygenation, so controlled hypotension poses no significant functional impairment to central nervous system and exerts no effect on the prognosis of patients [4, 6].

Currently, frequently used controlled hypotension drugs include volatile anesthetics, vasodi-

lator, calcium channel blocker, α1 adrenoceptor blocker, and β adrenoceptor blocker. Sevoflurane for controlled hypotension in craniocerebral operation is safer than other volatile anesthetics. Volatile anesthetics are usually not used alone for controlled hypotension, and their separate use is limited to short-term blood pressure reduction operations. Dexmedetomidine is a α_2-adrenergic receptor agonist, whose controlled hypotension function usually takes effect through anti-sympathetic action by activating the locus coeruleus neuron α_{2A} receptor in the brain stem, which prevents sympathetic excitation induced by controlled hypotension [7]. During blood pressure reduction, patients show relatively stable heart rate and blood pressure without reflex hypertension or tachycardia, which has certain protective effect on important organs such as heart and brain during the preoperative period [8].

Controlled hypotension refers to reducing MAP to 70% of basic blood pressure through human factors and ensuring sufficient oxygen supply to vital organs for normal metabolism and waste discharge [9, 10]. The effects of controlled hypotension on the renal function are as follows: when MAP is reduced to 70% of the basic blood pressure, renal blood flow is reduced in direct proportion to decreased MAP, and renal perfusion pressure is decreased accordingly, which is not enough to maintain the glomerular filtration rate, but can help to maintain the normal renal metabolism [11]. Dexmedetomidine can reduce renal inflammatory response during controlled hypotension, thus protecting the renal function.

Some studies have confirmed that dexmedetomidine combined with sevoflurane can effectively maintain patients' hemodynamic stability with a good anesthetic effect in anesthesia of hysteroscope operation and general anesthesia operation of pediatric inguinal hernia, and it is an ideal anesthesia induction method for surgery [12, 13]. However, there are few studies on the two drugs combined for controlled hypotension in craniocerebral operation. Therefore, this study aimed to explore dexmedetomidine combined with sevoflurane in controlled hypotension and the effects of different blood pressure reduction degrees on the renal function of patients during craniocerebral operation.

Materials and methods

Clinical data

This experiment was approved by the Ethics Committee of The Second Affiliated Hospital of Guangxi Medical University. All patients signed informed consent forms. A total of 90 patients (male:female = 55:35, age: 40-60 years) admitted from January 2018 to January 2019 who had undergone craniocerebral operation under general anesthesia were analyzed retrospectively.

Inclusion criteria: (1) Patients meeting craniocerebral operation standards [14]: Those with acute epidural hematoma >30 mL and temporal hematoma >20 mL require immediate craniotomy to remove hematoma, and those with acute epidural hematoma <30 mL, temporal hematoma <20 mL, the maximum thickness <15 mm, midline shift <5 mm, glasgow coma scale (GCS) score >8 points and without focal cerebral lesions symptoms and signs can be treated conservatively. Those patients should be treated with craniamphitom hematoma clear operation immediately once they show clinical consciousness change, high intracranial pressure, pupil change or CT hematoma enlargement. (2) Patients between 40 and 60 years old. (3) Patients in class I-II according to the American Society of Anesthesiology (ASA) classification.

Exclusion criteria: Patients with renal function impairment, cardiopulmonary insufficiency or blood coagulation dysfunction before operation.

Grouping

The 90 enrolled patients were analyzed retrospectively, and divided into three groups (Groups A, B and C), 30 patients in each group. Group A and Group B were injected with dexmedetomidine intravenously through a syringe pump and inhaled more sevoflurane after trauma craniotomy for controlled hypotension. MAP of Group A and Group B was maintained at 50-55 mmHg and 60-65 mmHg, respectively, and Group C was not treated with controlled hypotension.

Anesthesia scheme

The pressure of all patients was measured by arteria radialis puncture under local anesthesia

Table 1. Comparison of general information of patients

	Group A (n = 30)	Group B (n = 30)	Group C (n = 30)	F/χ^2	P
Age (year)	45.6±5.1	43.3±4.8	44.3±4.4	1.678	0.066
Gender (male/female)	12/18	11/19	15/15	1.184	0.553
Hemorrhage during operation (mL)	28.32±8.54	29.33±7.84	28.73±6.47	0.132	0.877
Intraoperative colloidal input (mL)	559.35±123.13	556.53±130.85	557.36±128.84	0.004	0.996
Preoperative comorbidities				2.250	0.690
Hypertension	5	4	3	0.582	0.747
Diabetes	4	5	2	1.549	0.461
Operation time (min)	88.35±5.54	85.35±5.77	85.34±4.95	3.062	0.052
Anesthesia time (min)	65.46±4.75	64.85±5.04	66.65±4.46	1.120	0.331
Amount of sevoflurane (mL)	38.34±2.35	39.23±2.85	38.66±2.23	0.982	0.379
Duration of controlled hypotension (min)	35.65±7.24	36.75±8.13	0	0.553	0.582

after peripheral vein catheterization, multilead electrocar diagram establishment, and oxygen saturation monitor connection.

Anesthesia induction: Patients were given oxygen for 2 min in advance, and then were injected intravenously with midazolam (0.05 mg/kg, Jiangsu Nhwa Pharmaceutical Co., Ltd.), propofol (2 mg/kg, Beijing Fresenius Kabi Pharmaceutical Co., Ltd.), cisatracurium (0.2 mg/kg, Jiangsu Heng Rui Pharmaceutical Co., Ltd.), and fentanyl (0.01 mg/kg, Yichang Humanwell Pharmaceutical Co., Ltd.) for stable anesthesia induction.

During operation, the patients were injected with propofol and remifentanil (Yichang Humanwell Pharmaceutical Co., Ltd.) through target-controlled infusion, and the concentrations of them in plasma were maintained at 1.5-3 μg/L and 8 ng/L, respectively. Meantime, the anesthesia of patients was maintained with inhalation of 2% sevoflurane.

Blood pressure reduction during operation

After patients' dura mater was opened, controlled hypotension was performed as follows: the intravenous injection rates of propofol and remifentanil, the oxygen flow inhaled by patients in each group were maintained unchanged; the sevoflurane (Shanghai Hengrui Pharmaceutical Co., Ltd.) concentrations of vaporizers in Group A and Group B were adjusted to 4% and 6%, respectively, and the two groups were injected intravenously with dexmedetomidine (Jiangsu Heng Rui Pharmaceutical Co., Ltd.) at 5 μg/kg/min to maintain the MAP of Group A and Group B at 50-55 mmHg and 60-65 mmHg, respectively. During administration, the patients were given 0.2 mg atropine when their heart rate dropped to 50 beats/min.

Outcome measures

The MAP of patients at the beginning of blood pressure reduction (T0), 60 min after pressure reduced to target pressure (T1), 60 min after blood pressure reduction stopped (T2) and 24 h after blood pressure reduction stopped (T3) was recorded, respectively. Arterial blood was sampled from patients of each group at the above four time points, and their creatinine, blood urea nitrogen, cystatin C, and glomerular filtration rate were compared.

Statistical analysis

Statistical analysis was carried out on data using SPSS 19.0. Enumeration data were expressed as the frequency number and frequency, and compared between groups using the chi-square test. Measurement data were expressed as the mean ± standard deviation ($\bar{x}$ ± sd), and comparison among multiple groups and pairwise comparison should be subject to the analysis of variance and Bonferroni post hoc test. Duration of controlled hypotension was analyzed by the t test. $P<0.05$ indicates a significant difference.

Results

General data

There were no significant differences in age, sex, operation time, and intraoperative colloidal input among the three groups (All $P>0.05$). See **Table 1**.

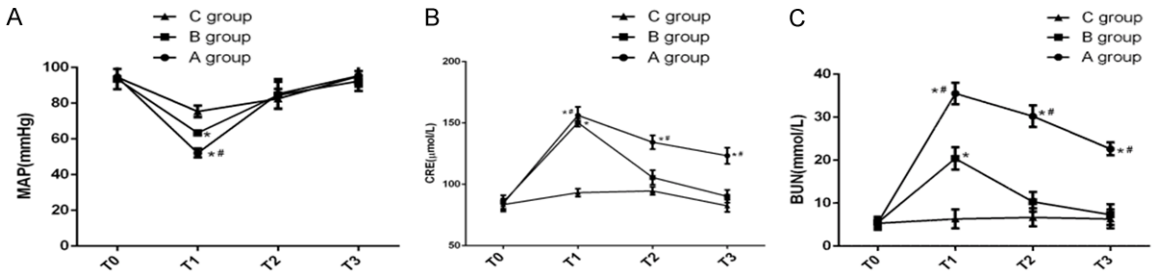

Figure 1. Mean arterial pressure, Creatinine level and Urea nitrogen level. A: Mean arterial pressure; B: Creatinine level; C: Urea nitrogen level. Compared with Group C, *P<0.05; compared with Group B, #P<0.05. MAP: mean arterial pressure; T0: the beginning of blood pressure reduction; T1: 60 min after pressure reduced to target pressure; T2: 60 min after blood pressure reduction stopped; T3: 24 h after blood pressure reduction stopped.

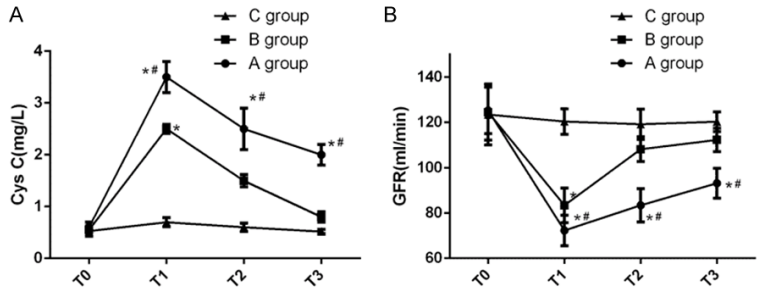

Figure 2. Cystatin c and Glomerular filtration rate. A: Cystatin c; B: Glomerular filtration rate. Compared with Group C, *P<0.05; compared with Group B, #P<0.05. Cys C: Cystatin c; T0: the beginning of blood pressure reduction; T1: 60 min after pressure reduced to target pressure; T2: 60 min after blood pressure reduction stopped; T3: 24 h after blood pressure reduction stopped.

Mean arterial pressure and heart rate

There was no significant difference in MAP at T0 among the three groups, and the highest MAP at T1 was seen in Group C, followed by Groups B and A (all *P*<0.05). Group A and Group B showed significantly lower MAP at T1 than that at T0 (both *P*<0.05). At T2 and T3, there was no significant difference in MAP among the three groups (all *P*>0.05). See **Figure 1A**.

Renal function

Creatinine level: At T0, there was no significant difference in creatinine level among the three groups. At T1, Group A and Group B showed significantly elevated creatinine level compared with Group C, and Group A showed a higher creatinine level than Group B (all *P*<0.05). At T2 and T3, Group A showed a significantly higher creatinine level than Group B and Group C (both *P*<0.05), but there was no significant difference between Group B and Group C. See **Figure 1B**.

Urea nitrogen level: At T0, there was no significant difference in urea nitrogen level among the three groups. At T1, Group A and Group B showed a significantly elevated urea nitrogen level compared with Group C, and Group A showed a significantly higher urea nitrogen level than Group B (all P<0.05). At T2 and T3, Group A showed a significantly higher urea nitrogen level than Group B and Group C (both *P*<0.05), and Group B and Group C had no significant difference. See **Figure 1C**.

Cystatin C: At T0, there was no significant difference in cystatin C level among the three groups. At T1, Group A and Group B showed a significantly elevated cystatin C level compared with Group C, and Group A showed a significantly higher cystatin C level than Group B (all *P*<0.05). At T2 and T3, Group A showed a significantly higher cystatin C level than Group B and Group C (both *P*<0.05), and Group B and Group C had no significant difference. See **Figure 2A**.

Glomerular filtration rate: At T0, there was no significant difference in glomerular filtration rate among the three groups. At T1, Group A and Group B showed a significantly decreased glomerular filtration rate compared with Group C, and Group A showed a lower glomerular filtration rate than Group B (all *P*<0.05). At T2 and T3, Group A showed a significantly lower glomerular filtration rate than Group B and Group C (both *P*<0.05), and Group B and Group C had no significant difference. See **Figure 2B**.

Discussion

Controlled hypotension is first applied in clinic by Gardner. It is a technique that uses various antihypertensive drugs to purposely reduce the blood pressure, control the blood pressure reduction degree and duration according to specific conditions, and create good conditions for surgical operations to reduce blood transfusion [15, 16]. Its main purpose is to reduce intraoperative blood loss under the premise of ensuring oxygen supply to vital organs, and to help to quickly return blood pressure to normal level after reducing blood pressure. The key to this technique is to ensure blood perfusion in tissues and protect organs. In theory, as long as the blood volume is normal and MAP exceeds 4.3 kappa (32 mmHg), microcirculation perfusion can be maintained normal, without giving rise to O_2 deficiency. MAP of 50-65 mmHg is set as the lowest limit for controlled hypotension in clinic practice. In this study, controlled hypotension was maintained at two ranges, 60-65 mmHg and 50-55 mmHg. Both the two ranges were in an effective controlled hypotensive range, but they had different effects on the prognosis after renal injury [17, 18].

In this study, dexmedetomidine and sevoflurane were used in combination for controlled hypotension, which had relatively reliable blood pressure reduction effect. The infusing rate of dexmedetomidine and the concentration of sevoflurane were adjusted to control the pressure of the target within a safe range. This study found that sevoflurane combined with dexmedetomidine can also improve the haemodynamic stability and lower the circulatory function of patients, and it could meet the surgical requirements better under the premise of ensuring normal blood flow and oxygen supply. One study by Zhang et al. found that dexmedetomidine combined with propofol and remifentanil in controlled hypotension can improve blood flow stability and reduce intraoperative blood loss [19]. In this study, the mechanism of sevoflurane for controlled hypotension was to dilate peripheral vessels and reduce cardiac afterload, which basically had no effect on cardiac output, because it had little inhibition on myocardial contractility. This study controlled the blood pressure at different low pressure ranges by controlling intravenous infusing rate of dexmedetomidine and inhaled concentration of sevoflurane, all of which can make the controlled hypotension within a safe range.

Renal function and hypertension are interactional, because abnormal renal function can cause an increase in blood pressure, and long-term increase in blood pressure can also give rise to abnormalities in renal function [20]. Dexmedetomidine suppresses the sympathetic activity and causes renal artery dilatation, resulting in a decrease in blood pressure [21]. Dexmedetomidine protects the renal function during controlled hypotension. In addition to mainly suppressing hemodynamic fluctuations caused by catecholamine, it also utilizes the self-regulation function of renal blood flow to protect the renal function. When the systolic pressure drops to 75 mmHg, the glomerular filtration rate declines, which contributes to sufficient oxygen supply and dilation of the renal blood vessels, thus protecting the renal function [22]. Jo et al. found that dexmedetomidine adopted for controlled hypotension for a long time in craniocerebral operation caused transient reversible damage of urea nitrogen and creatinine 2 h after surgery, but this damage was slowly restored within 24 h [23]. This study found that at 60 min and 24 h after controlled hypotension, renal function symptoms were significantly relieved, creatinine, urea nitrogen and cystatin C concentrations were gradually decreased, and glomerular filtration rate was significantly increased, which were consistent with the above findings.

This study has certain limitations, such as discontinuity of observation time points and renal function observation. We will further refine controlled hypotension process and time points after blood pressure reduction is stopped, so as to more clearly observe the dynamic changes of the renal function during controlled hypotension. In addition, we will further explore the molecular mechanisms and pathways underlying the effects of controlled hypotension on the renal function.

Dexmedetomidine combined with sevoflurane is effective in blood pressure reduction in craniocerebral operation. Controlled hypotension to 50-55 mmHg can cause reversible decrease of glomerular filtration function, and 60-65 mmHg is appropriate, so controlled hypoten-

sion to 60-65 mmHg is worthy of clinical application.

Disclosure of conflict of interest

None.

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