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Original Article

Effect of dexmedetomidine hydrochloride combined with limb remote ischemic preconditioning on quality of recovery from anesthesia in patients undergoing thoracoscopic lobectomy

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Abstract: Objective: To discuss the effect of limb remote ischemic preconditioning combined with dexmedetomidine hydrochloride on quality of recovery from anesthesia in patients undergoing thoracoscopic pulmonary lobectomy. Methods: A total of 40 patients underwent selective thoracoscopic lobectomy were divided into control group (group C) and limb remote ischemic preconditioning combined with dexmedetomidine treatment group (group ORD) by random number table method. in group ORD, 15 min after the completion of tracheal intubation, the blood flow of right upper limb was blocked for 5 min, and the perfusion was restored for 5 min (repeated 3 times); then ischemic preconditioning was performed, at the same time, intravenous infusion of 0.5 μg/kg dexmedetomidine was performed for 15 min and continued at a speed of 0.5 μg/(kg•h) until the end of the surgery. There was no limb remote ischemic preconditioning in group C, while intravenous infusion was performed with equal volume of normal saline. In the two groups, radial artery blood-gas analysis was performed before anesthesia induction (T1), after anesthesia (T2) and at the moment of palinesthesia (T3); *P* (A-a) DO2 and oxygenation index (OI) were calculated. The recovery quality and complications in the two groups were observed and recorded; the indexes included the recovery time of spontaneous respiration, time of eye opening, extubation time as well as the occurrence of postoperative bucking, restlessness, pain, nausea, vomiting, shivering and other complications during the recovery. Results: Compared with group C, the OI were increased and the respiratory indexes were decreased in group ORD at T2 and T3 (all $P<0.05$). There was no statistical difference in OI and respiratory index between the two groups at T1 (both $P>0.05$). The recovery time of spontaneous respiration, time of eye opening and extubation time between the two groups were similar (all $P>0.05$). The incidences of postoperative bucking, restlessness and pain 30 min after T3 in group ORD were lower than those in group C (all $P<0.05$). The incidences of shivering, nausea and vomiting in the two groups were similar (both $P>0.05$). Conclusion: The quality of recovery from anesthesia and the safety during recovery period can be improved in patients undergoing thoracoscopic pulmonary lobectomy when treated with dexmedetomidine hydrochloride combined with limb remote ischemic preconditioning.

Keywords: Dexmedetomidine, limb remote ischemic preconditioning, thoracoscopic pulmonary lobectomy, recovery from anesthesia

Introduction

Since the thoracoscopic lobectomy was used for the treatment of non-small cell lung cancer (NSCLC) in the early 1990s, the application of thoracoscopy, as a representative of the minimally invasive technique, in the diagnosis and treatment of lung disease was gradually expanded, and the surgical technology was becoming mature as well; currently, thoracoscopy is also used in complicated plastic operation involving the reconstruction of bronchial, pulmonary vascular and other structures [1-4]. Thus, in recent years, thoracoscopic lobectomy has won a lot of favor from the clinicians and lung disease patients in need of surgery. Its main advantage is great decrease of trauma in patients, so that patients get faster recovery after surgery and shorter hospital stays. At the same time, some complications occurred in patients received thoracoscopic lobectomy, mainly including pulmonary complications which impact postopera-

tive respiratory function. Studies have shown that the application of remote ischemic preconditioning in patients undergoing thoracoscopic lobectomy can reduce lung injury and achieve the lung protection effect with a promotion of rapid rehabilitation [2, 3]. At present, studies indicate that continuous intravenous infusion of dexmedetomidine hydrochloride combined with simultaneous limb remote ischemic preconditioning during perioperative period can improve the clinical rehabilitation after thoracoscopic lobectomy [5-8]. However, there were few researches studying the effect of the above combination on anesthesia recovery period in patients undergoing thoracoscopic lobectomy. In this study, patients underwent selective thoracoscopic lobectomy were treated with dexmedetomidine combined with limb remote ischemic preconditioning, and the effect during the recovery from anesthesia was observed.

Materials and methods

Case selection and grouping

This study was approved by the Ethics Committees of our hospital and the informed consent was obtained from patients or their families. A total of 40 patients underwent elective thoracoscopic lobectomy from August 2016 to June 2017 were enrolled in this study. Random number table method was adopted to equally divide these patients into control group (group C) and limb remote ischemic preconditioning combined with dexmedetomidine treatment group (group ORD), with 20 cases in each. Inclusion criteria: Patients with lobectomy indications, such as NSCLC (clinical stage I) and benign lung disease (pulmonary inflammatory pseudotumor, bronchiectasis, pulmonary aspergillosis, pulmonary sequestration, pulmonary tuberculoma, pulmonary cyst); patients with ASA grade I or II; patients with no basic disease; patients didn't suffer from systemic infection and pulmonary infection recently; patients didn't receive radiotherapy, chemotherapy, and treatment of glucocorticoids, antibacterial agents, immunosuppressant. Exclusion criteria: Patients at the age younger than 18 or older than 76; patients with heart, lung, liver or kidney dysfunction; patients with analgesic abuse; patients with a history of psychosis or dementia; patients unwilling to cooperate. All the surgeries were performed by the same group of surgeons.

Intervention measures

Group ORD: Dexmedetomidine hydrochloride treatment was carried out after tracheal intubation in anesthesia induction; intravenous infusion of 0.5 μg/kg dexmedetomidine hydrochloride was performed for 15 min, and then it was continued at a speed of 0.5 μg/(kg•h) until the end of pulmonary lobectomy [2].

After anesthesia induction and before one-lung ventilation, the right upper extremity was performed with remote ischemic preconditioning. The operating procedures were as follows: tying a tourniquet on the right upper limb near the armpit, inflating the tourniquet until the pressure reaching 200 mmHg, maintaining the pressure level for 5 min to block the right upper extremity blood flow, then loosening the tourniquet for 5 min, circulating the inflating and loosening for 3 times.

Group C: After tracheal intubation in anesthesia induction, the intravenous infusion of normal saline (equal to the volume of dexmedetomidine in ORD group) was carried out until the end of pulmonary lobectomy. There was no limb remote ischemic preconditioning performed before conventional one-lung ventilation.

Brief introduction of anesthesia method

Patients in both groups received general anesthesia with tracheal intubation. The induced drugs included midazolam (0.05 mg/kg), sulfentanyl (0.5 μg/kg), propofol (1.5 mg/kg) and cisatracurium (0.2 mg/kg). Three minutes after drug intravenous injection, the left double-lumen endotracheal tube was inserted, after that, the bronchofibroscope was used to check and determine whether the tube was in the appropriate position, and adjust it timely. The remifentanil (0.10-0.20 μg/kg/min), propofol (3-5 mg/kg/h) and cisatracurium (0.08-0.10 mg/kg/h) were used for intraoperative maintenance, and the value of bispectral index was maintained around 50 (40 to 60). During two-lung ventilation, the parameters of mechanical ventilation were set as follows: tidal volume (10-12 ml/kg), inspiratory/expiratory (1/2), breathing rate (10-12 times/min), fraction of inspired oxygen (80-100%), end-expiratory partial pressure of carbon dioxide (35-45 mmHg, by adjusting the respiratory rate). During one-lung ventilation, the tidal volume was 8-10 ml/kg; breathing rate was 12-15 times/min; the re-

Table 1. Patients' general information in two groups

Groups	Group C	Group ORD	t/χ^2	*P* value
Cases (n)	20	20	0	1
Male (n, %)	10 (50%)	11 (55%)	0.31	0.81
Age (years old)	33.7±6.9	32.9±7.5	0.39	0.78
BMI (kg/m^2)	20.1±2.8	19.6±3.2	0.71	0.38
ASA Grade I (n, %)	9 (45%)	10 (50%)	0.41	0.62

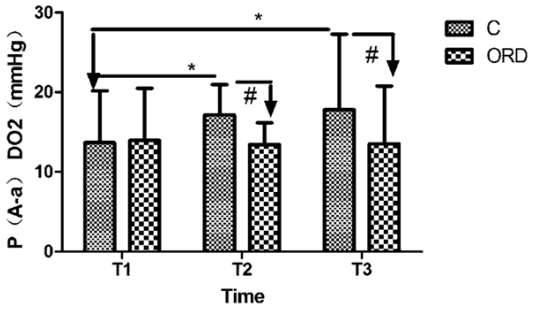

Figure 1. Changes of *P* (A-a) DO2 in patients at different time points Note: $^*P$<0.05 indicated that the comparison between T2, T3 and T1 in group C was statistically significant. $^\#P$<0.05 suggested that the comparison between T2, T3 in Group ORD and T2, T3 in group C was statistically significant.

Table 2. Comparison of P (A-a) DO2 at different time points in two groups ($\bar{x}$ ± sd, mmHg)

Groups	Group C	Group ORD	t/χ^2	*P* value
Cases (n)	20	20	0	1
T1	12.9±7.6	12.7±8.1	1.32	0.23
T2	14.3±7.9	12.1±6.8	5.02	0.025
T3	17.8±9.5	13.5±7.3	6.61	0.012

maining parameters kept unchanged. The double-lumen endotracheal tube intubation was replaced by single-lumen endotracheal tube intubation for sputum suction and lung inflation after skin suture and sternal closure. Then the patients were sent to the post anesthesia care unit. The tracheal intubation would not be removed until well recovery of autonomous respiration, consciousness and muscle tension.

Observation index and evaluation standard

Observation index: The radial artery blood samples were collected, and the blood gas was measured before anesthesia induction (T1), after the anesthesia (T2) and at the moment of palinesthesia (T3), respectively; P (A-a) DO2 and OI values were calculated and compared between the two groups. Besides, the postoperative palinesthesia indexes of patients in both groups were recorded, which included the autonomous respiration recovery time, time of eye opening, extubation time and the incidence of bucking, restlessness, pain, shivering, nausea and vomiting in patients within 30 min after palinesthesia.

Evaluation standard: Firstly, the bucking was evaluated and scored by four-point method: one point referred to no bucking; two points referred to mild bucking (one or two times); three points referred to moderate bucking (three or four times); four points referred to severe bucking (more than five times). Patients who got 1-2 points were identified as no bucking and could tolerate the endotracheal tube; patients who get 3-4 points were identified as bucking and the endotracheal tube was intolerable. Secondly, there were five levels of restlessness score according to the patients' clinical symptoms: one point, patients slept peacefully and were unresponsive to the external stimulations; two points, patients were sober with certain responses to stimulations, but remained calm; three points, patients were sober with accurate responses to stimulations and were emotional and irritable; four points, patients were uncontrollably crying and shouting, and they were hard to comfort; five points, patients were manic agitation with confusion and delirium, and were hard to be restrained. Patients who got 1-2 points were identified as no restlessness; patients who got 3 points were identified as mild and moderate restlessness; patients who got 4-5 points were identified as severe restlessness. The calculation of restlessness rate only included patients with score of 4-5. Thirdly, the pain score was evaluated by visual analogue scale. With a total score of ten points, zero point indicated no pain; one to three points indicated mild pain that could be tolerated; four to six points indicated moderate pain that influenced patients' sleep but still tolerated; seven to ten points indicated severe pain that was unbearable and influenced patients' sleep.

Statistical processing

SPSS19.0 statistical software was used for data processing and statistical analysis. The normal distribution of measurement data was

Table 3. Comparison of OI at different time points in two groups ($\bar{x}$ ± sd, mmHg)

Groups	Group C	Group ORD	t/χ^2	*P* value
Cases (n)	20	20	0	1
T1	425.6±27.6	421.3±28.4	1.12	0.32
T2	372.6±34.6	405.8±37.1	7.88	0.005
T3	387.1±35.9	413.5±37.8	6.13	0.016

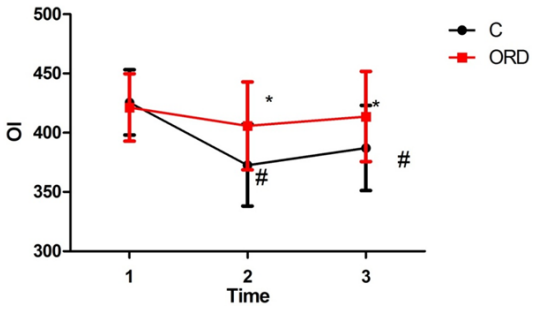

Figure 2. Comparison of the changing tendency of OI at different time points in two groups of patients Note: In group C, when T2 and T3 compared with T1, $^{*}P<0.05$; when T2 and T3 in group ORD compared with the same time point in group C, $^{\#}P<0.05$.

expressed as mean ± standard deviation ($\bar{x}$ ± sd); the t-test was used to compare the mean values between groups. The enumeration data were expressed as percentage (%); the chi-square test was used for the comparison between groups. The repeated measurement data which were measured at different time points were analyzed by variance analysis for repeated measurement. The differences were statistically significant when $P<0.05$.

Results

Comparison of general information in two groups

The differences of patients' general information between two groups were not significant (all $P>0.05$), and the data were comparable. See **Table 1**.

Comparison of P (A-a) DO2 at different time points in two groups

There was no significant difference in patients' *P* (A-a) DO2 at T1 in two groups ($P>0.05$). At T2 and T3, *P* (A-a) DO2 of patients in group ORD were much less than that in group C, and the differences were statistically significant (both $P<0.05$). In group C, compared with T1, *P* (A-a) DO2 at T2 and T3 were gradually increased and apparently higher with statistically significant ($P=0.032$, $P=0.022$). In group ORD, the changes of *P* (A-a) DO2 at different time points were not obvious; compared with T1, the increases of *P* (A-a) DO2 at T2 and T3 were not significant ($P>0.05$). See **Figure 1** and **Table 2**.

Comparison of OI at different time points in two groups

At T1, the comparison of OI between two groups of patients was not significant ($P>0.05$). The decreases of OI in group ORD at T2 and T3 were significantly less than those in group C (both $P<0.05$). In group C, compared with T1, OI at T2 and T3 were significantly decreased ($P=0.034$, $P=0.041$). In group ORD, the changes of OI at different time points were not obvious; compared with T1, the decreases of OI at T2 and T3 were not sharp (both $P>0.05$). See **Table 3** and **Figure 2**.

Comparison of postoperative recovery time from anesthesia and incidences of complications

The postoperative recovery related time from anesthesia (spontaneous respiration recovery time, eye opening time and extubation time) between two groups were not significant (all $P>0.05$). See **Table 4**. Compared with group C, the incidences of adverse reactions (bucking, restlessness and pain) during postoperative recovery period in group ORD were obviously decreased ($P=0.035$, $P=0.023$ and $P=0.031$ respectively). No marked difference was found in the incidences of shivering, nausea and vomiting in the two groups (both $P>0.05$). See **Table 5**.

Discussion

The thoracoscopic pulmonary lobectomy often causes lung injury and pulmonary hypoperfusion because of intraoperative one-lung ventilation [9]. Remote ischemic preconditioning was usually applied to reduce the oxidative damage of lung and improve postoperative gas exchange in the pulmonary lobectomy of lung cancer patients; studies have proved that limb remote ischemic preconditioning can reduce the occurrence of lung injury and pulmonary complications, such as intraoperative or post-

Table 4. Postoperative recovery time from anesthesia in two groups (min)

Groups	Group C	Group ORD	T	*P* value
Spontaneous respiration recovery time	12.56±3.65	11.98±3.24	0.465	0.512
Eye opening time	18.75±3.45	17.69±3.62	0.476	0.423
Extubation time	25.76±5.34	23.71±4.74	0.208	0.165

Table 5. Comparison of adverse reactions in two groups (n, %)

Groups	Group C	Group ORD	t/χ^2	*P* value
Restlessness	8 (40%)	1 (5%)	5.03	0.023
Bucking	10 (50%)	2 (10%)	4.42	0.035
Nausea and vomiting	5 (25%)	4 (20%)	1.21	0.682
Pain	8 (40%)	2 (10%)	4.65	0.031
Shivering	3 (15%)	2 (10%)	0.25	0.851

operative pulmonary gas exchange [10-12]. Experiments have proved that the application of dexmedetomidine can provide protective effect on lung injury [13, 14]. The results of this study showed that compared with T1, the increases of *P* (A-a) DO2 in group ORD at T2 and T3 were significantly less than those in group C (both $P<0.05$); the decreases of OI at T2 and T3 in group ORD were also significantly less than those in group C (both $P<0.05$); the *P* (A-a) DO2 and OI in group ORD varied little at different time points (all $P>0.05$). The results indicated that the combined application of remote ischemic preconditioning and dexmedetomidine influenced less on pulmonary ventilation and oxygenation function in patients underwent pulmonary lobectomy. The possible reason might be that remote ischemic preconditioning and dexmedetomidine could prevent lung injury, thus reduce the effect of lung injury on pulmonary ventilation and oxygenation function.

Dexmedetomidine hydrochloride is a new highly selective α2-adrenaline receptor agonist with good sedation, hypnosis, analgesia, anxiolytic and sympathetic nerve block effects; the pharmacokinetic properties of dexmedetomidine hydrochloride don't change with age; there is no significant pharmacokinetics difference in young, middle-aged and elderly patients; this medicine has obvious clinical advantages of short half-life, less medication dose and high safety [15]. In addition, limb remote ischemic preconditioning might protect tissues and organ by antioxidation and inhibiting inflammatory factors. Studies have showed that intravenous infusion of dexmedetomidine hydrochloride during the spinal anesthesia can not only provide good sedation for patients, but also prolong the anesthetic action time and improve the postoperative analgesic effects in patients [16, 17]. In this study, in group ORD, after the completion of trachea cannula during anesthesia induction, we performed combined use of limb remote ischemic preconditioning and intravenous infusion of dexmedetomidine hydrochloride until the end of pulmonary lobectomy. At the same time, patients in group C were only treated with intravenous infusion of normal saline for contrast analysis. The results showed that there was no significant difference in recovery related time between the two groups (both $P>0.05$), but compared with group C, the incidence of bucking, restlessness and postoperative pain in group ORD decreased significantly (all $P<0.05$), which indicated that combined use of remote ischemic preconditioning and dexmedetomidine could achieve the intraoperative sedation of patients, but would not lead to respiratory depression and longer extubation time; more importantly, it could reduce the incidence of restlessness, bucking and pain of patients after operation, as well as improve the anesthetic quality and safety in recovery period; therefore, it was worthy of clinical recommendation, which was basically consistent with other reports. The study of He et al. showed that the application of remote ischemic preconditioning could reduce lung injury by inhibiting the inflammatory reaction during one-lung ventilation in patients undergoing thoracic surgery; consequently, the airway acidification was reduced [18]. The study of Yu et al. showed that limb remote ischemic preconditioning had pulmonary protective effect during one-lung ventilation in patients undergoing radical resection of esophageal cancer, but the clinical significance was not obvious [19]. The findings of Afonso et al. showed that dexmedetomidine hydrochloride combined with upper limb ischemic preconditioning could inhibit inflammatory cells, reduce the consumption of

superoxide dismutase, lighten the lung injury induced by ischemia-reperfusion, and affect little on pulmonary ventilation and oxygenation function of patients underwent thoracoscopic pulmonary lobectomy [20].

In summary, the treatment of dexmedetomidine hydrochloride combined with limb remote ischemic preconditioning can improve the quality of anesthesia recovery in patients who underwent thoracoscopic lobectomy, and affect little on pulmonary ventilation and oxygenation function; it can also improve the comfort degree and the anesthesia quality of patients, resulting in more stable recovery and higher safety in recovery period. However, because of the small sample capacity of this study, further experiments of bigger sample size and refining grouping are needed to demonstrate the validity of the conclusion, and to further explore the corresponding mechanism.

Disclosure of conflict of interest

None.

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