Clinical application and effect of dexmedetomidine in combination with continuous positive airway pressure on one-lung ventilation in lung surgery of elder patients

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Abstract: In this study, 126 elder patients who underwent thoracic surgery under general anesthesia were divided into three groups randomly, i.e. dexmedetomidine group, positive ventilation group and combination group. All patients received varying strategies in addition to the one-lung ventilation, and changes in oxidative stress and indicators of inflammation at different time points were observed. In comparison to the dexmedetomidine group and the positive ventilation group, patients in the combination group at T2-3 had lower levels of malonaldehyde, cortisol, C-reaction protein, interleukin-6 (IL-6) and tumor necrosis factor α in serum ($p<0.05$); one day after surgery, the incidence of complications in lungs of patients in the combination group was significantly lower than those in the dexmedetomidine group and the positive ventilation group ($p<0.05$). Dexmedetomidine in combination with continuous positive airway pressure can alleviate the oxidative stress and inflammation of lung tissues in one-lung ventilation during the thoracic surgery of elder patients, thus, reducing the incidence of postoperative complications.

Keywords: Thoracic surgery, dexmedetomidine, continuous positive airway pressure, oxidative stress, inflammation.

INTRODUCTION

Thoracic surgery, a kind of surgery with large trauma, requires one-lung ventilation to guarantee the vision and operation space on the operative side (Li *et al*., 2008). Nevertheless, reduction in blood supply of lung caused by atrophy of lung cancer on the other side further results in hypoxic pulmonary vasoconstriction; pulmonary re-expansion again induces massive generation of oxygen radical due to the supplement of oxygen in response to hypoxia, thus generating oxidative stress. Meanwhile, mechanical ventilation can cause a potent release of inflammatory factors, so as to induce the inflammatory responses (Karzai *et al*., 2009). Oxidative stress, together with inflammatory responses, give rise to the acute lung injury, putting the life of patients at risk. Elder patients, due to declines in tolerance and metabolism functions, have become a high-risk population of acute lung injury in one-lung ventilation. According to a study (Sato *et al*., 2000), it is pointed out that continuous positive airway pressure can sustain the suitable dilation of lung on the non-ventilation side, which is conducive to reducing the oxidative stress caused by one-lung ventilation. Dexmedetomidine, a highly selective α2-adrenergic agonist, can activate the cholinergic anti-inflammatory pathway, decreases the tension of sympathetic nerves and reduces the inflammation of patients in perioperative period effective (Weerink *et al*., 2017). In this study, we aimed to investigate the effect of dexmedetomidine in combination with the continuous positive airway pressure on the oxidative stress and inflammation of lung in one-lung ventilation during the thoracic surgery of patients, so as to evaluate the clinical efficacy and provide theoretical evidence for clinical practice.

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MATERIALS AND METHODS

General material

A total of 120 elder patients who planned to undergo thoracic surgery under general anesthesia in this hospital between May 2015 and June 2017 were selected in this study. All patients were categorized as ASA II or III, and underwent surgery in the morning lasting not shorter than 1 h and not longer than 4 h. In these patients, there were 60 males and 60 females aged between 65 and 77 years old with an average age of (71.2±6.9) years old; body mass index (BMI) ranged between 18.5 and 25.3 kg/m2 with an average of (20.6±3.3) kg/m2. Besides, forced vital capacity (FVC) of all patients was higher than 80% of the predictive value, and the forced expiratory volume in 1 s higher than 70% of the predictive value. Two weeks before surgery, all patients were required to quit smoking, and patients with chronic diseases, including hypertension, mellitus diabetes, chronic obstructive pulmonary disease, restrictive lung disease, blood disease or other metabolic disorders, were excluded from this study. With random digit table, patients were divided into three groups, i.e. the dexmedetomidine group (n=40), positive ventilation group (n=40) and combination group (n=40). No statistical significance was identified in comparisons of the age, BMI and grades among three groups ($p>0.05$; table 1). This study had been approved by the Ethic Committee of the hospital and informed consents of patients had been obtained before study.

Methods

Food, water and drugs were withdrawn at 8 h before surgery. After delivery into the surgery room, patients were monitored by electrocardiogram, measurements of blood pressure and heart rate, as well as the blood gas analysis. Moreover, venous channel was established in the upper right limb, and under local anesthesia, right arteria radialis puncture was performed for collecting blood samples and invasive arterial blood pressure monitoring; while depth of anesthesia was monitored using Narcotrend. Anesthetic induction: intravenous injection of 0.08-0.12 mg/kg midazolam, 0.1-

1.0μg/kg sufentanil, 0.2-0.6mg/kg etomidate and 0.15mg/kg atracurium besylate. Mechanical ventilation was carried out through the catheter inserted through the mouth, and the position was located by the fiber bronchoscope using following parameters: rate of oxygen flow 1.0-1.5 L/min, oxygen concentration 100%, breathe frequency 10-13 time/min, respiratory quotient 1:2, and PETCO2 35-40 mmHg. Maintenance of anesthesia: intravenous injection of 4-8 mg/kg/min propofol, and intermittent injection of 5-10 μg sufentanil and 7 mg cisatracurium besylate with adjustment of the injection rate of propofol, Narcotrend index being maintained between 40 and 50 and mean arterial pressure (MAP) and heart rate (HR) within 20% of premium value. Intravenous injection of Lactated Ringer's Solution and 6% hydroxyethyl starch (130/0.4) was performed during the operation in volume ratio of 3:1, and injection of propofol was suspended at 5 min before the end of surgery. In the operation, corresponding measures were taken in response to the changes in MAP and HR to maintain the stability of blood pressure and homeostasis. In the dexmedetomidine group and the combination group, dexmedetomidine (at a dose of 0.3 μg/kg SFDA, Approval No.H20110085, Manufacturer: Jiangsu Nhwa Pharmaceutical Co., Ltd.) was given intravenously for 10 min, followed by continuous intravenous injection at a rate of 0.3μg/kg/h till the closure. At the beginning, patients in three groups received one-lung ventilation, while for those in the positive ventilation group and the combination group, non-ventilation lung tissues were connected with the NLF-200A continuous positive airway pressure system (Superstar-med) with pressure being set as 2 cm H_2O. For hypoxemia during operation, two-lung ventilation was adopted only for patients with airway and catheter being in good apposition and not valid for aspiration of sputum and positive end expiratory pressure. Additionally, patients who underwent blood infusion were excluded. After surgery, patient controlled intravenous analgesia (PCIA) was given with VAS being maintained within 3 min.

Evaluation indexes

At the time of skin incision (T0), 90 min since one-lung ventilation (T1), the end of surgery (T2) and 24 h after surgery (T3), venous blood was drawn to detect the concentration of malonaldehyde in serum using thiobarbituric acid method, and levels of cortisol, C-reactive protein, interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α) in serum with reagents provided by BD (USA). Incidence of complications in lung of three groups was compared at 1 d and 7 d after surgery.

STATISTICAL ANALYSIS

SPSS 17.0 software was used to perform statistical analysis. Measurement data were presented as mean ± standard deviation (X ± s) and one-way analysis of variance (ANOVA) was adopted for comparisons among group, while ANOVA of repeated measurement was carried out for comparison between different time points in one group. Enumeration data were expressed as ratio and Fisher exact test or chi-square test was performed in intergroup comparison. $p<0.05$ suggested that the difference had statistical significance.

RESULTS

General data

In the dexmedetomidine group, there were 2 patients with hypoxemia who received two-lung ventilation, and the incidence was 5%; no such cases were identified in other two groups. No statistical significance was discovered in comparisons of the duration of one-lung ventilation, surgery duration and bleeding amount among three groups ($p>0.05$). In the dexmedetomidine group and the combination group, usage of propofol of patients was less than that of the positive ventilation group with statistically significant difference ($p<0.05$; table 2).

Changes in the oxidative stress and inflammatory indexes at different time points of patients Compared with the levels at T0, a significant increase was identified in concentration of malonaldehyde in patients of three groups at T2-3, and augmentations in levels of cortisol, CRP, IL-6 and TNF-α in serum were also observed at T1-3 ($p<0.05$); in comparison with the dexmedetomidine group or positive ventilation group, decreases were found in levels of malonaldehyde, cortisol, CRP, IL-6 and TNF-α in serum at T2-3 ($p<0.05$; table 3).

Incidence of pulmonary complications in patients of three groups at different time points

One day after surgery, incidence rates of hypoxemia, pulmonary infection and pulmonary atelectasis in the patients of the combination group were all lower than those in the dexmedetomidine group and the positive ventilation group. Incidence rate of pulmonary complications of patients in the combination group was10.0%, lower than 36.8% of dexmedetomidine group and 30.0% of the positive ventilation group ($p<0.05$). At the 7^{th} day after surgery, pulmonary infection was not observed in patients of the combination group, but found in other two groups with one patient in

Table 1: Comparisons of the general data among three groups (x ± s)

Group	n	Age (y)	Gender (male/female)	BMI (kg/m^2)	ASA grade (II/III)
Dexmedetomidine group	40	70.8±5.8	17/23	19.3±3.9	25/15
Positive ventilation group	40	72.1±6.6	19/21	20.1±4.2	28/22
Combination group	40	70.3±5.2	21/19	21.2±4.7	30/10
χ2		0.571	0.752	0.721	1.387
p		0.552	0.673	0.475	0.483

Table 2: General data of surgery of patients (x ± s)

Group	n	Ventilation duration (min)	Surgery duration (min)	Bleeding amount (mL)	Usage of propofol (mg)
Dexmedetomidine group	38	128.5±34.5	159.5±34.5	296.2±18.6	995.4±223.3
Positive ventilation group	40	138.3±26.4	163.3±30.7	307.4±19.2	1197.1.4±245.1*
Combination group	40	135.2±35.1	167.4±26.4	302.1.2±20.7	983.2±233.5$^{\#}$
χ^2		1.276	1.187	2.218	10.393
p		0.274	0.301	0.109	0

Note: *$p<0.05$ *vs.* the dexmedetomidine group; #$p<0.05$ *vs.* the positive ventilation group.

Table 3: Changes in the oxidative stress and inflammatory indexes at different time points of patients (x ± s)

Item	Group	T_0	T_1	T_2	T_3
Malonaldehyde (mmol/mL)	Dexmedetomidine group	5.05±0.18	5.10±0.21	7.46±0.26^{a+}	5.99±0.38^{a+}
	Positive ventilation group	5.01±0.23	5.07±0.28	7.39±0.30^{a}	5.95±0.32^{a}
	Combination group	4.95±0.17	5.09±0.19	6.53±0.20$^{a*\#}$	5.00±0.31$^{*\#}$
Cortisol (pg/mL)	Dexmedetomidine group	24.48±7.4	40.38±13.1^{a}	76.28±26.7^{a+}	53.68±13.7^{a+}
	Positive ventilation group	23.78±7.1	39.68±14.0^{a}	73.88±24.6^{a}	50.58±12.4^{a}
	Combination group	24.18±7.6	38.58±13.8^{a}	62.58±20.4$^{a*\#}$	39.38±1.56$^{a*\#}$
CRP (pg/mL)	Dexmedetomidine group	4.20±0.31	6.30±0.46^{a}	10.20±2.42^{a+}	8.14±1.56^{a+}
	Positive ventilation group	4.41±0.50	6.23±0.50^{a}	9.74±3.11^{a}	7.96±1.40^{a}
	Combination group	4.35±0.44	6.16±0.52^{a}	5.73±0.67$^{A*\#}$	5.32±1.22$^{a*\#}$
IL-6 (pg/mL)	Dexmedetomidine group	61.68±9.7	126.48±26.6^{a}	162.38±40.4^{a+}	134.58±37.6^{a+}
	Positive ventilation group	59.58±7.6	134.58±32.4^{a}	170.28±37.5^{a}	138.38±28.5^{a}
	Combination group	60.08±5.2	116.78±45.2^{a}	120.48±23.7$^{a*\#}$	96.48±24.3$^{a*\#}$
TNF-α (pg/mL)	Dexmedetomidine group	31.48±2.6	43.68±3.7^{a}	56.18±6.5^{a+}	45.28±5.8^{a+}
	Positive ventilation group	32.38±4.7	42.28±5.6^{a}	59.38±7.7^{a}	44.18±8.7^{a}
	Combination group	33.18±5.4	43.38±4.5^{a}	46.38±4.4$^{a*\#}$	34.48±6.6^{a8a3}

Note: $^{a}p<0.05$ *vs.* levels at T0; $^{+}$ for difference with statistical significance; $^{*}p<0.05$ *vs.* dexmedetomidine group; #$p<0.05$ *vs.* positive ventilation group.

Table 4: Incidence of pulmonary complications of patients after operation [n (%)] each group (table 4).

Group	n	1 d				7d			
		Hypoxemia	Pulmonary infection	Pulmonary atelectasis	Total	Hypoxemia	Pulmonary infection	Pulmonary atelectasis	Total
Dexmedetomidine group	38	6 (15.8)	7 (18.4)	1 (2.6)	14 (36.8)	0	1 (2.6)	0	1 (2.6)
Positive ventilation group	40	5 (12.5)	7 (17.5)	0	12 (30.0)	0	1 (2.5)	0	1 (2.5)
Combination group	40	1 (2.5)$^{*\#}$	3 (7.5)$^{*\#}$	0*	4 (10.0)$^{*\#}$	0	0$^{*\#}$	0	0$^{*\#}$

Note: *$p<0.05$ *vs.* the dexmedetomidine group; #$p<0.05$ *vs.* positive ventilation group.

DISCUSSION

As a non-physiological ventilation mode in thoracic surgery, one-lung ventilation remains conducive to the operation. However, it makes patients susceptible to the acute lung injury during the reoxygenation of lung tissues in response to hypoxia (Birdas *et al*., 2006). Especially for elder patients, declined physiological functions and poor tolerance to surgery and hypoxia are two factors inducing the acute lung injury during one-lung ventilation (Xu *et al*., 2008). Meanwhile, various factors emerging from one-lung ventilation during the thoracic surgery may also act on the oxidative stress and inflammation. Thus, in this study, aiming to highlight the roles of dexmedetomidine and continuous positive airway pressure in the oxidative stress and inflammation caused by one-lung ventilation, special controls were exerted on the surgical protocol, operators and surgical duration, so as to maximally remove the effect of other factors on the results of study(Kernan *et al*., 2011). Dose of dexmedetomidine was determined in reference to the clinical experience and literatures (Ito *et al*., 2005), while the pressure of continuous positive airway ventilation was also confirmed according to the conclusion of a study (Al-Shehri *et al*., 2014). Meanwhile, considering the clinical significance of 2 cm H^2O, it was also taken as one of the indicators. In light that most of operators could finish the operation within 90 min for patients with one-lung ventilation, relative indicators were determined at this time point.

Malonaldehyde, cortisol and CRP are indicators reflecting the oxidative stress, in which malonaldehyde can directly indicate the degree of lipid peroxidation (Rosato *et al*.,2012). In this study, the results showed that compared with the levels at T0, a significant increase was identified in concentration of malonaldehyde in patients of three groups at T2-3, and augmentations in levels of cortisol and CRP in serum were also observed at T1-3 (p<0.05); in comparison with the dexmedetomidine group or positive ventilation group, decreases were found in levels of malonaldehyde, cortisol and CRP in serum at T2-3 (p<0.05). These results suggested that oxidative stress in varying degrees appeared in patients of three groups. However, dexmedetomidine in combination with continuous positive airway pressure can decrease the levels of malonaldehyde, cortisol and CRP, suggesting that combined strategy excels the single use in alleviating the oxidative stress in one-lung ventilation for elder patients in thoracic surgery (Sato *et al*., 2005). IL-6 and TNF-α are indexes reflecting the inflammation, and monitoring these indexes can help operators be aware of the inflammatory responses during one- lung ventilation (Cheng *et al*., 2014). The results of this study indicated that compared with the levels at T0, augmentations in levels of IL-6 and TNF-α in serum were also observed at T1-3 (p<0.05); in comparison with the dexmedetomidine group or positive ventilation group, decreases were found in levels of IL-6 and TNF-α in serum at T2-3 (p<0.05), suggestive of the inflammation in patients of all three groups. But, combined strategy was more effective in relieving the inflammation during one-lung ventilation than single use for elder patients in thoracic surgery. Also, it was also found that one day after surgery, incidence rate of pulmonary complications of patients in the combination group was 10.0%, lower than 36.8% of dexmedetomidine group and 30.0% of the positive ventilation group (p<0.05). At the 7th day after surgery, pulmonary infection was not observed in patients of the combination group, but found in other two groups with one patient in each group, which indicated that oxidative stress and inflammation were sufficiently suppressed in one-lung ventilation during thoracic surgery of elder patients by dexmedetomidine in combination with continuous positive airway pressure, which conduces to reduce the incidence of postoperative complications, improve the prognosis and protect the lung tissues.

In conclusion, in one-lung ventilation during thoracic surgery of elder patients, dexmedetomidine in combination with the continuous positive airway pressure can reduce the oxidative stress and inflammation in lung tissues and the incidence of postoperative complications, which conduces to improve the prognosis and protect the lung tissues.

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