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Low dose of esketamine combined with propofol in painless fibronchoscopy in elderly patients

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Abstract

To explore the effects and safety of low dose of esketamine combined with propofol in elderly patients undergoing fibronchoscopy. Eighty elderly patients who underwent painless fibronchoscopy in our hospital from June 2021 to September 2021 were recruited,and randomly divided into experimental group (esketamine 0.15mg/ kg + propofol 1mg/ kg) and control group (sufentanil 0.1 μg/ kg + propofol 1mg/ kg), with 40 cases in each group. There were significant differences in MAP, HR and SpO_2 of T2, T3 and T4 between the experimental and control groups ($P < .05$). Besides, there were significantly differences on the trend of change between the 2 groups, with a small and relatively stable fluctuation in the experimental group ($P < .05$). Compared with the control group, the total dosage of propofol in the experimental group was significantly lower, and the number of vasoactive drugs, the incidence of respiratory depression and bronchospasm were significantly lower ($P < .05$). There was no significant difference in microscopic examination time, wake-up time, visual analogue score, and agitation, mental symptoms, increased secretion, nausea and vomiting, choking cough and laryngeal spasm during awakening period between the 2 groups. The incidence of total adverse reactions in the experimental group were strongly lower than those in control group. ($P < .05$). Low dose of esketamine combined with propofol can be safely used for fibronchoscopy in elderly patients, with good effects, more stable respiration and circulation, and low incidence of adverse reactions.

Abbreviations: MOAA/S = modified observer assessment of alertness/sedation scale, VAS = visual analogue score.

Keywords: bronchospasm, elderly patients, esketamine, painless fibronchoscopy, sufentanil

1. Introduction

Fiber bronchoscopy (fibronchoscopy) has been widely used in clinical practice, which is an important method for the diagnosis, treatment and rescue of lung diseases.[1] Because the respiratory tract has a strong defensive and rejection function, fibronchoscopy can easily cause severe coughing, breath holding, and bronchospasm during the operation, even lead to cardiovascular and cerebrovascular accidents and life-threatening events in severe cases.[2] In order to reduce the discomfort and fear of patients during the examination, and to facilitate the operation procedure for endoscopists, intravenous anesthesia with propofol in combination with a short-acting opioid is usually performed in clinical practice.[3] However, the combination of these drugs may lead to an increased risk of respiratory and circulatory inhibition in elderly patients, who are the main population to receive the examination of fibronchoscopy, and have a poor oxygen reserve capacity and circulatory function. Esketamine is a novel intravenous anesthetic drug with potent analgesic effects, which has the characteristics of rapid onset of action, rapid awakening, mild respiratory depression, and dilated bronchi.[4] Studies have shown that anesthesia with propofol and esketamine is safe and reliable, with shorten anesthesia time, good postoperative cognitive function recovery, and relatively mild adverse effects.[5] The study aimed to explore the effect and safety of low-dose esketamine combined with propofol for fibronchoscopy in elderly patients.

2. Materials and methods

2.1. Subjects

This was a prospective, randomized, controlled study. From June 2021 to September 2021, a total of 80 patients who underwent painless fibronchoscopy in our hospital were selected and randomly divided into experimental group (esketamine 0.15mg/ kg + propofol 1mg/ kg) and control group (sufentanil 0.1 μg/ kg + propofol 1mg/ kg), according to the computer randomized number table method, with 40 cases in each group. The inclusion

YF and TD contributed equally to this work.

The written consent was received from all participants.

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Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

All patients were informed and signed informed consent voluntarily. This study was approved by the ethics committee of the Wuhan First Hospital and complied with the guidelines outlined in the declaration of Helsinki were followed.

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criteria were as followings: age over 65 years; American society of anesthesiologists (ASA) Grades I to III; pulse oxygen saturation ≥ 90% without oxygen inhalation; body mass index (BMI) within 18.5~26.5kg/ m^2; received the procedures of fibronchoscopy and alveolar lavage. The exclusion criteria included: severe cardiac and pulmonary insufficiency; allergic or addicted to esketamine or its active ingredients; uncontrolled hypertension (systolic/diastolic blood pressure exceeding 180/100 mm Hg at rest); had a high risk of increased intracranial pressure; glaucoma and others with increased intraocular pressure; poor treatment of hyperthyroidism; had mental illness. This study was conducted in accordance with the ethical principles of human trials, and was approved by the Ethics Committee of Wuhan First Hospital. Written informed consent was obtained from all participants.

2.2. Procedures

All patients routinely fasted for 8 hours, and had no drinking for 4 hours before surgery. The patients received anesthesia visit the day before the procedure, to assess the patient's cardiopulmonary function, prejudge the possibility of difficult airway, and finish the examination of Electro cardiogram, chest x-ray and blood test. The fibronchoscopy room was equipped with Philips monitors, Drager anesthesia machines, defibrillators, double-tube laryngeal mask, visible laryngoscope, and emergency endotracheal intubation box. Medications including sufentanil, esketamine, propofol, atropine, ephedrine, uradil, and epinephrine were prepared preoperatively.

Experiment group: The intravenous channel was opened after the patients entering the fibronchoscopy room. Oxygen were inhaled through nasal catheters, with the oxygen flow of 3~6 L/minute, and ECG, blood pressure and pulse oximetry monitoring were used. Prior the fibronchoscopy, patients in the experimental group were given a small dose of esketamine (0.15 mg/kg).[6] Propofol 1 mg/kg was then injected intravenously. After 1 minute of administration, the amount of propofol was adjusted according to the modified observer assessment of alertness/sedation scale (MOAA/S) to maintain MOAA/S at 2-point level. If the score was > 2 points, 0.5mg/kg propofol was added. While if the score was < 1 or airway obstruction was occurred, the infusion of propofol was stopped. The criteria of MOAA/S scoring was 5 points: responds readily to name spoken in norma tone, 4 points: lethargic responses to name spoken in normal tone, 3 points: responds only after name is called loudly or repeatedly, 2 points: responds only after mild prodding or snaking, 1 point: responds only after painful trapezius squeeze, 0 point: no response after painful trapezius squeeze.[7] When MOAA/S reached 2 points, the fibronchoscopy was entered through the nasal approach, and lidocaine hydrochloride 1 mg/kg was sprayed at the supraglottic and endotracheal, respectively. The fibronchoscopy were then withdrawn, and continued the examination after 2 to 3 minutes until the anesthesia was fully effective.[8] During the procedure, the patient's vital signs were closely observed. When HR was < 50 beats/minute, intravenous injection of atropine 0.5 mg; if the MAP increase exceeded 20% of the basal value, intravenous injection of urapidil 10 mg; while if the MAP reduction exceeded 20% of the base value, ephedrine 6 mg was given intravenously. When the SPO_2 was < 90%, the jaw was supported to help ventilation, and when it was < 80%, the surgeons would stop the operation, temporarily withdraw the fibronchoscopy, give manual assisted ventilation, and continue the examination after the SPO_2 was higher than 90%. Patients was sent to the resuscitation chamber for observation postoperatively, with oxygen inhalation and monitoring. Visual simulation score (VAS) was recorded 10 minutes after the patient woke up (0 points for no discomfort, 5 points for moderate discomfort but bearable, and 10 points for being very uncomfortable and unbearable).[8]

Control group: Preoperative preparation was the same as that of experimental group. Sufentanil 0.1 μg/kg was used for anesthesia induction, while other treatments during the operation was in consistent with the experimental group.

2.3. Observational measurements

The hemodynamics, including MAP, HR, and SpO_2 of the 2 groups before anesthesia induction (T1), immediately after induction (T2), fibronchoscopy entry (T3), fibronchoscopy withdrawn (T4), and waken up (T5) were recorded and compared. The microscopic examination time, wake-up time, total dosage of propofol, VAS score 10 minutes after awakening were compared between the 2 groups. In addition, perioperative adverse reactions, including agitation during awakening, psychiatric symptoms (delirium, delusions, hallucinations, etc.), increased discharge, nausea and vomiting, choking, use of vasoactive drugs, respiratory depression (oxygen needed with the support of jaw or mask), bronchospasm and laryngospasm were recorded.

2.4. Statistical analysis

SPSS statistical software (Version 20.0, CA) was used for data processing and analysis. The measurements with normal or approximate normal distribution were described by mean ± standard deviation (x ± s), and the comparison between groups was analyzed with the paired *t*-test, intra-group comparison with ANOVA. The counting data were described as constitutive ratios or rates (%), and the intergroup comparisons were calculated by χ^2. $P < .05$ was regarded as statistically significant for the differences.

3. Results

3.1. General information

There were no significant differences between the 2 groups in age, sex, BMI and American society of anesthesiologists grading ($P > .05$), shown in Table 1.

3.2. MAP, HR and SPO_2

Changes of MAP, HR and SPO_2 at different time points between 2 groups were compared using repeated measurement design ANOVA. The results showed that there were significant

Table 1

The comparison of baseline characteristics between the 2 groups (n = 40, ±*s*).

Group	Age	Sex(M/F)		BMI	ASA Grade(N)		
		Male	Female		I	II	III
Experiment	70.5 ± 14.5	22/18		22.0 ± 2.3		13/15/11	
Control	71.2 ± 15.8	21/19		23.2 ± 2.5		12/15/14	
χ^2/t	2.115	0.210*		0.121		0.462*	
P	0.250	0.652		0.645		0.110	

* value for χ^2.

differences of MAP, HR and SPO_2 at various time points within each group (F = 12.342, 5.231 and 7.520, respectively, P = .000). Furthermore, the differences of MAP, HR and SPO_2 between the experimental and control groups at timepoints T2, T3, and T4 were significant (F = 9.280, 4.320, and 6.231, P = .000). The changes of MAP, HR and SPO_2 of the 2 groups were different (F = 13.321, 6.023 and 5.380, respectively, both P = .000), and the fluctuation range of experimental group was smaller, compared with control group (Table 2).

3.3. Measurements during the procedure

There was no significant difference in the microscopic examination time, wake-up time, and VAS score 10 minutes between the 2 groups (P > .05). However, the total dosage of propofol administrated in the experimental group was significantly reduced, compared with the control group (P < .05), shown in Table 3.

3.4. Perioperative adverse reactions

There were no significant differences with agitation during the waken up period, psychiatric symptoms, increased secretions, nausea and vomiting, choking, and laryngospasm between the 2 groups (P > .05). However, compared with the control group, the incidence of vasoactive drug use, respiratory depression and bronchospasm in the experimental group were significantly reduced (P < .05). In addition, the total adverse reactions perioperatively in the experimental group were significantly lower than control group (P < .05), as shown in Table 4.

4. Discussion

Fibronchoscopy is 1 of the most important methods for respiratory diseases diagnosis and treatment, which is usually conducted for the early detection of bronchial and pulmonary diseases.[9] Elderly patients are the main population for fibronchoscopy, who are sensitive to anesthetic drugs because of myocardial contractility inhibition and blood vessels dilation, resulting in hypotension.[10] In addition, the alveolar surface area, lung compliance, and the sensitivity of respiratory center to hypoxia and high carbon dioxide in older patients are reduced, leading to the predisposition to hypoxemia during perioperative phase.[11] Effective, safe and satisfactory analgesic options for fibronchoscopy in elderly patients are still being explored.

The new esketamine is ketamine of the dextran, which has a higher affinity with NMDA receptors and μ opioid receptors. Esketamine has a stronger analgesic effect, with only 1/2 dosage of ketamine needed, shows the characteristics of fast effective onset, rapid elimination, light respiratory function inhibition, no obvious airway secretions, and lower circulatory agitation, and avoids the disadvantages of ketamine Thus, esketamine has a unique advantage in anesthesia, especially for surgeries with short duration. A clinical trial at Xiangya Hospital showed that a single dose of esketamine (0.5 mg/ kg) injected within 10 seconds was safe and effective for painless gastrointestinal endoscopy, with a recovery time of 9 minutes and 11.5 minutes for directional force recovery.[12] Another research showed that small doses of esketamine (0.15 mg/ kg) in combination with propofol could be used for endoscopic retrograde cholangiopancreatography (ERCP), which reduced the total usage of propofol.[6] Although the commonly reported dose of esketamine was 0.5 mg/ kg, this dose of esketamine seemed to have comparable incidence of side effects with ketamine. Considering that esketamine has a stronger analgesic sedation effect, and a small dose of esketamine (0.15 mg/ kg) combined with propofol could be

Table 2

MAP, HR, and SPO_2 changes at various time points between the 2 groups (n = 40, ±s).

Group	MAP					HR					SPO_2				
	T_1	T_2	T_3	T_4	T_5	T_1	T_2	T_3	T_4	T_5	T_1	T_2	T_3	T_4	T_5
Experiment	86.3 ± 9.2	81.2 ± 8.3①②	82.1 ± 10.5①	83.4 ± 8.8①	84.6 ± 8.7	78.5 ± 8.6	69.6 ± 7.5①②	86.5 ± 10.5②	87.5 ± 8.9	79.6 ± 7.5②	98.5 ± 6.7	95.9 ± 4.6①	95.5 ± 6.1①	95.7 ± 6.3①	97.5 ± 6.8
Control	85.9 ± 10.1	69.2 ± 6.8②	72.3 ± 7.5	73.9 ± 8.2	83.5 ± 8.3②	76.8 ± 7.9	59.6 ± 6.1②	86.5 ± 10.5②	86.6 ± 8.5	77.5 ± 7.3②	98.1 ± 6.6	92.8 ± 5.1②	92.2 ± 5.2②	91.7 ± 5.8②	96.9 ± 6.2②

Note: (1) compared to control group, P < .05; (2) compared to T1, P < .05; (3) compared to T2, P < .05; (4) compared to T3, P < .05; (5) compared to T4, P < .05.

Table 3

Examination time, wake-up time, propofol dosage and VAS score between the 2 groups (n = 40, ±*s*).

Group	Examination time (min)	Wake-up time (s)	Propofol dosage (mg/kg)	VAS score
Experiment	12.5	3.1	2.1	2.7
Control	11.6	3.3	1.2	3.1
t	-0.150	1.650	-0.732	0.850
P	0.261	0.380	0.020	0.125

VAS = visual analogue score.

used in outpatient surgical anesthesia scenarios. Therefore, it is speculated that esketamine may have a potential advantage for accelerate wake-up, and shorten postoperative cognitive function recovery, with no increase of adverse effects.[17] Thus, for elderly patients undergoing fibronchoscopy.

Table 4

Incidence of adverse reactions in the perioperative period [n = 40, case (%)].

Group	N	AA	PS	ID	NV	Choking	VD	RD	BS	LS	Overall
Control	40	0 (0.0)	0 (0.0)	2 (5)	6 (15)	7 (17.5)	15 (37.5)	12 (30)	5 (12.5)	0	47
Experiment	40	1 (2.5)	0 (0.0)	3 (7.5)	5 (12.5)	8 (20)	4 (10)	2 (5)	1 (2.5)	0	24
χ^2		-	-	1.200	0.820	0.680	1.050	0.351	4.320	-	2.300
P		-	-	0.560	0.812	0.623	0.035	0.023	0.016	-	0.015

AA = agitation during awakening, BS = bronchospasm, ID = increased discharge, LS = laryngospasm, NV = nausea and vomiting, PS = psychiatric symptoms (delirium, delusions, hallucinations, etc.), VD = use of vasoactive drugs, RD = respiratory depression.

The results of this study showed a decrease in the total usage of propofol, which was consistent with previous finding in elderly patients who had received the examination of gastrointestinal endoscopy.[13] At the same time, the combination of esketamine and propofol reduced the incidence of hypotension in elderly patients, and the frequency of vasoactive drugs used, which might be caused by the sympathomimetic effect of esketamine that offset the circulatory inhibition effect of propofol and opioids, and stabled the circulation. Evidence has shown that small doses of ketamine combined with propofol, opioids, and sedative analgesics such as benzodiazepines could reduce adverse effects of respiratory circulation.[14] In this study, patients with esketamine combined with propofol did not have psychogenic adverse effects, including delirium and hallucinations during the wake-up phase, which was consistent with the previous findings published in 2017. The study explored the effects of ketamine on the prevention of postoperative delirium in the elderly patients, and found that small doses of ketamine neither prevent the occurrence of postoperative delirium, nor lead to an increased incidence of delirium.[15] The incidence of neurologic and psychiatric adverse effects after surgeries was low, which was dose-dependent, could be significantly reduced with the use of low doses.[16] Furthermore, in the study, the incidence of oxygen administration and bronchospasm in the experimental group was reduced, which might be related to the airway protection effect with esketamine, which could significantly inhibit airway reactivity and inflammation, relax the contraction of airway smooth muscle induced by various stimuli, and maintain the body's responsiveness to CO_2, with a slight effect on central respiratory motility. No case of laryngospasm was identified, which might be associated with a small dose of esketamine used in the study.

A recent study on the effects of propofol combined with esketamine on perioperative stress, inflammatory response, and postoperative cognition in elderly surgical patients confirmed that compared with propofol and sufentanil, propofol plus combined with esketamine could significantly reduce hemodynamic fluctuations, surgical stress, and inflammatory responses, elderly patients undergoing fibronchoscopy, escloramine may be a good option.

There were still several limitations in this study. First, the inhibitory effect of the drug combination regimens on cough reflex was not ideal. The local infiltrative anesthesia of supraglottic and endotracheal with lidocaine was required during the microscopic examination to reduce the incidence of choking cough to about 80%. In addition, the sample size was relatively small. Large sample studies were needed to confirm the findings and further explore the optimal effective dose of esketamine.

In summary, the small dose of esketamine combined with propofol can meet the sedative and analgesic needs of elderly patients undergoing fibronchoscopy, which has little impact on respiratory circulation and low incidence of adverse reactions.

Author contributions

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