Am J Transl Res 2023;15(1):563-572
www.ajtr.org /ISSN:1943-8141/AJTR0146892

Original Article

Effect of different doses of midazolam combined with fentanyl during painless bronchoscopy in adults

Qiaoqin Yan, Bingbing Sheng, Xiaoyan Huang, Kang Lin, Jie Lin, Xianhua Ye

Department of Anesthesiology, The First People's Hospital of Wenling, Taizhou 317500, Zhejiang, P. R. China

Received October 8, 2022; Accepted December 15, 2022; Epub January 15, 2023; Published January 30, 2023

Abstract: Objective: To investigate the clinical effect of different doses of midazolam combined with fentanyl during painless bronchoscopy in adult patients. Methods: In this retrospective study, a total of 200 patients who underwent painless bronchoscopy in The First People's Hospital of Wenling from January 2018 to January 2021 were selected as research subjects. These patients were assigned into an experimental group and a control group with 100 patients in each group. Patients from the experimental group were sedated with an intravenous infusion of 0.05 mg/kg midazolam and 0.2 μg/kg fentanyl, while patients from the control group were sedated using 0.1 mg/kg midazolam and 0.2 μg/kg fentanyl. The changes in heart rate (HR), saturation of pulse oximetry (SpO_2), systolic blood pressure (SBP), and diastolic blood pressure (DBP) before and at 10 minutes after administration were compared between the two groups. Ramsay sedation scale, RSS agitation scale, awaking time, incidence of adverse reactions, and anesthetic effects were also compared. Results: After medication, there was no significant difference in terms of HR, SBP, or DBP values between the two groups. The SpO_2 value in the experimental group was higher than that in the control group (96.93±1.10% vs. 94.78±0.83%, P<0.05). Ramsay sedation scale of patients from the experimental group after medication was (3.88±0.66), which was significantly higher than that of the control group (2.32±0.63), while RSS agitation score in the experimental group was (1.08±0.16), lower than that of the control group (2.32±0.63). The awaking time in the experimental group was shorter than that in control group (43.60±3.30 min vs. 50.19±4.45 min, P<0.05). Moreover, the incidence of mild cough or no cough in the experimental group was significantly better than in the control group (P<0.05). The overall incidence of adverse reactions in the experimental group was lower than that of the control group (5.00% vs. 13.00%, P<0.05). In addition, the anesthetic effect in the experimental group was better than that of the control group (90% vs. 80%, P<0.05). Conclusion: The use of 0.05 mg/kg midazolam combined with 0.2 μg/kg fentanyl in adult painless bronchoscopy has little effect on SpO_2 levels, possesses a good sedative and anesthetic effect, and reduces the awaking time, restlessness response, and adverse reactions.

Keywords: Midazolam, fentanyl, painless bronchoscopy, anesthetic effect

Introduction

Bronchoscopy is considered as the gold standard for the diagnosis and treatment of respiratory diseases. During the clinical examination, a slender bronchoscope is inserted into the lower respiratory tract through the patient's oral or nasal cavity. Through the observation of the bronchial cavity, the location of the lesion is determined, and then steps such as brushing, biopsy, and lavage are performed [1, 2]. Bronchoscopy can detect lung cancer, inflammatory lesions, tuberculosis and other respiratory diseases at an early stage, and make a differential diagnosis of the cause. In addition, during the treatment of patients with cancer, bronchoscopy is used to evaluate the clinical treatment effect. For palliative surgery of patients with advanced cancer, bronchoscopy makes the patient's airway more open which helps to improve the treatment effect.

In recent years, with improved anesthesia, many hospitals in China have implemented painless fiberoptic bronchoscopy, which is bronchoscopy under general anesthesia. This reduces the patient's nervousness and lack of cooperation, and relieves pain [3, 4]. Fentanyl is an opioid commonly used for general anesthesia. Fentanyl can quickly reach the blood-brain bar-

rier within one minute and decay rapidly in tissues and blood, so it has a rapid effect and a short maintenance time. Because of the above characteristics, Fentanyl is used in combination with other drugs in the induction of general anesthesia [5, 6]. Many studies revealed that opioids can inhibit the production and release of stress hormones such as catecholamines through the sympathetic-adrenomedullary axis, further reducing the stimulatory response caused by airway manipulation, decreasing the intensity of the stress response, and maintaining the stability of the body's hemodynamics [7]. Another study showed that opioids should not be used alone for bronchoscopic anesthesia [8]. Midazolam is a very fast-acting benzodiazepine drug. Midazolam injection has effects of anti-anxiety, sedation, hypnosis, anticonvulsion and muscle relaxation. Midazolam injection can be used as an adjuvant drug for preoperative sedation, spinal anesthesia and local anesthesia, and also is applied for sedative care in critically ill patients. In addition, midazolam is usually exploited in clinical diagnostic or therapeutic operations such as cardiovascular angiography, bronchoscopy, and gastrointestinal endoscopy [9, 10]. It was reported that a benzodiazepine plus opioid could better reduce the cough response and improve comfort and tolerability in contrast to benzodiazepine alone [11]. Recently, in New Zealand and Australia, a survey showed that 94% of pulmonologists used a two-sedative combination, and of these, 96% used the combination of midazolam and fentanyl [12]. In the United Kingdom, 89% of pulmonologists used sedation for bronchoscopy [13]. In China, data regarding low dose of midazolam combined with fentanyl for sedation during painless bronchoscopy in adult patients are not available. Moreover, the effects of midazolam combined with fentanyl during painless bronchoscopy remain controversial [14]. The purpose of the present study was to investigate the effects of different doses of midazolam combined with fentanyl during painless bronchoscopy in adult patients. The results of this study may provide evidence for use in clinical practice.

Materials and methods

Patients

This research was approved by the Ethics Committee of The First People's Hospital of Wenling. In this retrospective trial, 200 patients undergoing painless bronchoscopy in the Department of anesthesiology in our hospital between January 2018 and January 2021 were selected as participants. The inclusion criteria were as follows: patients who aged from 30 to 60 years old; patients who underwent anesthetic indications; patients in American Society of Anesthesiologists physical status of I or II; patients with body mass index between 18 kg/m^2 and 27 kg/m^2; patients received the treatment voluntarily. The exclusion criteria were as follows: patients who were suffered from congenital or other heart diseases; patients with hepatic or renal dysfunction, cardiac or cerebral insufficiency, or coagulation disorders; patients with a history of hypotension, tachycardia, glaucoma, bronchial asthma or snoring; patients with immune system disease or electrolyte disturbance; patients who were allergic to anesthetic, or received long-term use of opioids; patients under went bronchoscopy for more than half an hour; patients with contraindications to anesthetic drugs. The patients were scheduled to undergo painless bronchoscopy using different doses of midazolam combined with fentanyl. According to the medications they received, all the patients were assigned into a control group and an experimental group, with 100 cases in each group.

Anesthesia methods

Before painless bronchoscopy, the routine food and water fasting were for 5 h and 2 h, respectively. When patients were in the examination room, the peripheral venous channel in unilateral upper limb was open, and slow intravenous infusion of 500 ml of saline sodium chloride injection (No. H19994066, Baxter Healthcare (Shanghai) Co., Ltd.) was performed at the speed of 10 ml/min. The continuous oxygen inhalation (3-4 L/min) was also conducted. The electrocardiographic (EKG) monitoring was performed to record the vital signs such as heart rate (HR), oxygen saturation (SPO_2), systolic blood pressure (SBP) and diastolic blood pressure (DBP). The equipment including a respirator, invasive ventilator, endotracheal intubation, defibrillator and so on, and cardiopulmonary resuscitation-related rescue drugs were routinely prepared. Bronchial mucosal surface anesthesia was provided using 10 ml of 2% lidocaine (No. H31021071, Shanghai Zhaohui

Pharmaceutical Co., Ltd.) in the form of a nebulized inhalation.

In the experimental group, midazolam (No. H20113433, Jiangsu Jiuxu Pharmaceutical Co., Ltd.) was administered intravenously at 0.05 mg/kg, and fentanyl (No. H20113508, Jiangsu Nhwa Pharmaceutical Co., Ltd.) was given intravenously at 0.2 μg/kg. In the control group, midazolam was provided intravenously at 0.1 mg/kg, and fentanyl was given intravenously at 0.2 μg/kg. The sedative and analgesic medications were administered by an anesthesiologist. The bronchoscopy was performed when patients fell asleep, with steady breathing and no eyelash reflexes. During the examination, if the SpO_2 was lower than 90%, the patient's jaw was lifted, and they were called to take a breath while increasing the oxygen flow until the SpO_2 was raised. The bronchoscopy was terminated if SpO_2 continued to decrease and was lower than 80%. At the end of bronchoscopy, patients were awakened using 7 μg/kg flumazenil (No. H20113191, Yichang Humanwell Pharmaceutical Co., Ltd.). Patients went back to the inpatient ward or left the hospital when the Aldrete score was more than 9 points.

Observed outcomes

(1) Vital sign indicators including HR, SpO_2, SBP, and DBP were recorded before and at 10 minutes after the medication using EKG monitors. (2) Sedation status was evaluated 10 minutes after the medication using the Ramsay sedation scale [15]. To be specific, 1 point: patient shows anxiety and restlessness; 2 points: patient is quiet and cooperative; 3 points: patient only responds to instructions; 4 points: patient falls asleep, but has quick response when the glabella was slightly tapped and a loud shout was performed; 5 points: patient falls asleep with slow response when the glabella was slightly tapped and a loud shout was performed; 6 points: patient is in deep sleep and has no response to stimulation. Moderate sedation is from 2 points to 4 points, and within this range, higher scores indicate a better sedation effect. (3) Wakefulness state [16] was evaluated using RSS agitation scale. 0 point: patient is quiet; 1 point: patient has mild agitation, such as intermittent moan; 2 points: patient has continuous moan but not strong agitation in the limbs; 3 points: patient has severe agitation with vigorous struggle or shouting. Higher scores suggest a more obvious agitation [17]. (4) Cough conditions: were evaluated after waking up. The cough was graded severe, moderate, mild, or none according to a previous report [18]. (5) The adverse reactions in patients were recorded and compared between the two groups. The adverse reactions included nausea, vomitus, inappetence, restlessness and respiratory inhibition. (6) Anesthetic effects were evaluated. Excellent outcome: the glottis opened well and no choking or occasional cough while the bronchoscope was inserted. Good outcome was considered: the glottis opened well, and the bronchoscope entered relatively smoothly, but paroxysmal cough occurred 3-5 times. General outcome: the glottis opened not well, and patients still had nausea reflection. Also, the bronchoscope did not enter smoothly, and obvious paroxysmal cough occurred more than 7-8 times. Patients were restless, but there was no obvious cyanosis or suffocation. Poor outcome: the glottis did not open well, and patients still had reflux, the bronchoscope did not enter smoothly, with heavy paroxysmal cough and restlessness, and there were cyanosis and suffocation. Total excellent and good rate was calculated according to the following formula: Total excellent and good rate = (Number of excellent and good cases/total number of cases) × 100%.

Statistical evaluation

The SPSS 23.0 (IBM Corp., Armonk, NY, USA) was applied to analyze the collected data, and GraphPad prism 5.0 statistical software (GraphPad Software Inc., San Diego, CA, USA) was used as the graphic software in this study. Normally distributed quantitative data were expressed as mean ± standard deviation (SD). T test was used to examine the differences between the control group and experimental group. Counted data were presented as rate (%) and were analyzed using the χ^2 test. $P<0.05$ indicated a statistical difference.

Results

Comparison of general information between the two groups

In the control group, 49 patients were male and 51 were female. They had a mean age of 37.55±5.48 years old, a mean weight of

Table 1. Comparison of general information between the two groups

Value	Control group (n=50)	Experimental group (n=50)	t/χ^2 value	*P* value
Male/female (Cases)	49/51	52/48	0.180	0.671
Age (years)	37.55±5.48	37.53±5.51	0.026	0.979
Weight (kg)	63.48±1.40	63.51±1.37	0.153	0.878
Course of disease (d)	3.11±0.74	3.08±0.72	0.291	0.772
Type of disease (Cases)			0.251	0.578
Pneumonia	17	19		
Bronchiectasis infection	22	21		
Chronic obstructive pulmonary disease	28	26		
Pulmonary space-occupying	29	26		
Pulmonary tuberculosis	4	8		

63.48±1.40 kg/m^2, an average course of disease of 3.11±0.74 d, and there were 17 cases with pneumonia, 22 cases with bronchiectasis infection, 28 cases with chronic obstructive pulmonary disease, 29 cases with pulmonary space occupying lesion, and 4 cases with pulmonary tuberculosis. In the experimental group, 52 patients were male and 48 were female. They had an average age of 37.53±5.51 years old, an average weight of 63.51±1.37 kg/m^2, a mean course of disease of 3.08±0.72 d, and there were 19 cases with pneumonia, 21 cases with bronchiectasis infection, 26 cases with chronic obstructive pulmonary disease, 26 cases with pulmonary space occupying lesion, and 8 cases with pulmonary tuberculosis. No significant difference was observed in age, sex, weight, course of disease, or type of disease between the two groups (P>0.05, **Table 1**).

Comparison of vital signs between the two groups

Before medication, there were no statistical differences in HR, SpO_2, SBP, or DBP between the two groups. After medication, the control group had an average HR of 79.07±6.12/min, a mean SpO_2 of 94.78±0.83%, an average SBP of 114.04±5.40 mmHg and an average DBP of 75.86±7.91 mmHg. The experimental group had a mean HR of 78.86±5.52/min, a mean SpO_2 of 96.93±1.10%, a mean SBP of 115.81±5.54 mmHg, and a mean DBP of 75.06±7.59 mmHg. No significant difference was found after medication in HR, SBP, or DBP between the two groups. Significant difference was observed in SpO_2 index between the two groups (P<0.05), as shown in **Table 2**.

Comparison of sedation status and awake state between groups

In the control group, Ramsay sedation scale, RSS agitation scale, and awakening time were 2.32±0.63, 2.32±0.63, and 50.19±4.45 min, respectively. In the experimental group, Ramsay sedation scale, RSS agitation scale, and awakening time were 3.88±0.66, 1.08±0.16, and 43.60±3.30 min, respectively. After medication, Ramsay sedation scale in the experimental group was higher than that of control group, while RSS agitation scale and awakening time were significantly lower than in the control group, (all P<0.001), as described in **Table 3**.

Comparison of cough conditions between groups

As described in **Table 4**, in the control group, there were 21 cases with no cough, 36 cases with mild cough, 38 cases with moderate cough and 5 cases with severe cough, while in the experimental group, there were 41 patients with no cough, 22 patients with mild cough, 35 patients with moderate cough and 2 patients with severe cough. The difference was significant (P<0.05).

Comparison of adverse reaction between groups

As described in **Table 5**, in the control group, there were 2 cases with nausea, 2 cases with vomitus, 2 cases dizzy, 3 cases with inappetence, 2 cases with restlessness and 2 cases with respiratory inhibition, while in the experimental group, there were 1 case with nausea, 1

Table 2. Comparison of vital signs indexes between the two groups

Group	Cases	HR (Rate/min)				SpO_2 (%)			
		Before medications	10 min After medications	30 min After medications	10 min after withdrawal	Before medications	10 min After medications	30 min After medications	10 min after withdrawal
Experimental group	100	76.24±4.68	78.86±5.52	79.35±5.74	80.05±6.14	97.65±0.66	96.93±1.10	97.10±1.14	97.42±0.96
Control group	100	76.26±4.67	79.07±6.12	79.58±5.69	80.16±6.35	97.33±0.97	94.78±0.83	95.88±0.97	96.45±0.87
t value		0.145	0.350	0.275	0.452	0.586	4.383	2.154	1.062
P value		0.965	0.830	0.906	0.804	0.760	0.026	0.068	0.125
Group	Cases	SBP (mmHg)				DBP (mmHg)			
		Before medications	10 min After medications	30 min After medications	10 min after withdrawal	Before medications	10 min After medications	30 min After medications	10 min after withdrawal
Experimental group	100	123.49±3.65	115.81±5.54	118.75±6.12	120.19±6.64	76.13±8.32	75.06±7.59*	74.91±7.14	76.08±6.87
Control group	100	123.44±3.35	114.04±5.40	117.86±5.95	119.39±6.04	76.73±8.12	75.86±7.91*	75.08±7.37	76.65±6.96
t value		0.539	0.605	0.716	0.655	0.373	0.483	0.154	0.262
P value		0.771	0.698	0.653	0.674	0.822	0.796	0.942	0.918

Note: Compared to that before medications, *P<0.05. HR: Heart Rate; SpO_2: Oxygen Saturation; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.

Table 3. Comparison of sedation status and wakefulness state between the two groups

Group	Cases	Ramsay sedation scale	RSS agitation scale	Awakening time (min)
Experimental group	100	3.88±0.66	1.08±0.16	43.60±3.30
Control group	100	2.32±0.63	2.32±0.63	50.19±4.45
t value		17.097	19.077	11.895
P value		<0.001	<0.001	<0.001

Note: RSS: Ramsay Sedation Scale.

Table 4. Comparison of cough conditions between the two groups [*n* (%)]

Group	Cases	Severe	Moderate	Mild	No cough
Experimental group	100	2 (2.00)	35 (35.00)	22 (22.00)	41 (41.00)
Control group	100	5 (5.00)	38 (38.00)	36 (36.00)	21 (21.00)
χ^2 value			2.209		
P value			0.027		

Table 5. Comparison of incidence of adverse reaction between the two groups (n)

Group	Cases	Nausea	Vomitus	Dizzy	Inappetence	Restlessness	Respiratory inhibition	Overall adverse reaction rate (%)
Experimental group	100	1	1	1	1	0	1	5.00
Control group	100	2	2	2	3	2	2	13.00
χ^2 value								3.907
P value								0.048

Table 6. Comparison of anesthetic effects between the two groups (n)

Group	Cases	Excellent	Good	General	Poor	Excellent and good rate (%)
Experimental group	100	40	50	6	4	90.0
Control group	100	32	48	12	8	80.0
χ^2 value						3.922
P value						0.047

case with vomitus, 1 case dizzy, 1 case with inappetence and 1 case with respiratory inhibition. The overall adverse reaction rate in the experimental group was significantly lower than in the control group (5% vs. 13%, P<0.05).

Comparison of anesthetic effect between groups

As described in **Table 6**, in the control group, there were 32 cases with excellent effect and 48 cases with good effect, while in the experimental group, there were 40 cases with excellent 48 cases with good effect. The excellent and good rate in the experimental group was 90%, which was significantly higher in the control group (P<0.05).

Discussion

Ordinary bronchoscopic examination is performed when the patient is awake. During the examination, the bronchoscope passes through the glottis, trachea, and bronchi. The patient is prone to chest distress, shortness of breath, severe cough, airway spasm, arrhythmia, and cardiac arrest. Moreover, a survey suggested that patients were generally fearful and nervous during the inspection process, which had some impact on the bronchoscopy, usually leading to trembling, which interruption the examination, or inadequate results [19]. Painless bronchoscopy is considered a comfortable technique that allows patients to complete the entire bronchoscopy under sedation or anes-

thesia and close supervision [20]. During the inspection process, the patient has hsafety, physical and mental comfort, and the entire process is pain-free. During the examination, the patient has no obvious adverse reactions, which allows doctors to observe the lesions clearly and watch for flushing, biopsy, hemostasis and other functions accurately and efficiently. Painless bronchoscopy has the following three advantages: (1) Comfort: The inspection process is comfortable, and patients have no negative memories after waking up, and there is no fear of re-examination. (2) Safety: The anesthesiologist always stays during the inspection process. The endoscopic mask, laryngeal mask, and tracheal tube are all available to ensure safe airway and stable heart rhythm and circulation. (3) Convenience: Intravenous anesthetics take effect rapidly, with convenient administration, short action time, slight respiratory depression, and quick recovery after examination. Painless bronchoscopy meets the anesthetic need of medical services [21]. Bronchoscopy can detect the lesions in the airways and lungs in the form of endoscopy and obtain diagnostic specimens. Bronchoscopy can determine whether there arelesions in the bronchial mucosa, narrowing of bronchial lumen, or new organisms in the bronchial lumen. In addition to the detection of disease, bronchoscopy can also allow performance of bronchoalveolar lavage. The lavage fluid can be used to find out a lung infection or the type of pathogenic bacteria. Special staining or classification of cell technology in the bronchoalveolar lavage fluid can be used for preliminary identification of some diseases, such as preliminary differential diagnosis of hypersensitivity pneumonitis or interstitial lung disease. Lymph node or lung biopsy can also be taken through bronchoscopy to further clarify lung disease [22].

Fentanyl is an opioid analgesic drug that is mainly used to relieve pain in patients during surgery. It can also have a good analgesic effect in patients with postoperative incision pain [23]. It is rapidly hydrolyzed into non-pharmacologically active metabolites by non-specific esterases in blood and tissues, which do not depend on liver and kidney function. In clinical practice, it is usually used in combination with other drugs. The side effects of fentanyl can produce abdominal wall stiffness and breathing disorders. After using fentanyl, shallow breathing, reduced breathing frequency, and even apnea can occur through respiratory inhibition [24]. Sedation for the patient is done to reduce pain and anxiety, and provide amnesia for diagnostic procedures including endoscopy and interventional procedures that contribute to discomfort. Several clinical trials have been conducted using midazolam as procedural sedation, mostly for colonoscopy, upper gastrointestinal endoscopy and bronchoscopy [25]. Midazolam is a water-soluble benzodiazepine that can quickly pass through the blood-brain barrier. Midazolam is mainly metabolized in the liver, so liver dysfunction or hepatic metabolism enzymatic drugs such as calcium channel blockers can prolong the central inhibitory effect of midazolam [26]. The above characteristics and effects of midazolam make it an indispensable intravenous anesthetic that plays an important role in the entire perioperative period. In view of the special characteristics of pediatric patients and pregnant women, midazolam also shows unique advantages in pediatric and obstetric anesthesia. For example, pediatric patients are prone to crying and not cooperating before surgery, with a high incidence of postoperative delirium. Pregnant and lying-in women are anxious with a high stress level. Midazolam can effectively improve these problems that other drugs cannot address at present [27]. In addition, midazolam has a variety of dosage forms such as oral, intramuscular, intravenous, and rectal administration, which are suitable for application under various situations.

The results of this study showed that after medication, there was no significant difference in HR, SBP, or DBP indexes between the two groups, but the SpO_2 level in the experimental group was significantly higher than in the control group. Moreover, the experimental group had a higher Ramsay sedation score, lower RSS agitation score, and shorter awaking time than the control group, with significant differences. Through analysis, midazolam had a slight effect on the cardiovascular system in the body, and the clinical manifestations showed a mild increase in the HR, a mild decrease in systemic vascular resistance and mean arterial pressure, and a slight decrease in left ventricular filling pressure and stroke volume. Midazolam had no effect on myocardial

contractility. In addition, midazolam mainly has an inhibitory effect on the respiratory center and little effect on respiratory power [28, 29]. It can inhibit breathing to some extent, and the main clinical manifestations are the reduction of tidal volume, the increase of respiratory rate, and the shortening of expiratory time. Midazolam has no effect on functional residual capacity and residual lung capacity. Moreover, midazolam itself has no analgesic effect, but it can enhance the analgesic effect of other anesthetics. Midazolam possesses anxiolytic, hypnotic, anticonvulsant, muscle relaxant, and anterograde amnesia effects [30, 31]. Depending on the dose, different degrees of effects from anxiolytic to unconsciousness are produced. Midazolam can reduce the metabolic rate of brain tissue and constrict cerebral blood vessels, thereby decreasing cerebral blood flow. There is an obvious dose-dependency, but this dose-effect relationship has a ceiling effect. Midazolam can also reduce the blood flow velocity of the middle cerebral artery, increase vascular resistance, and have a protective effect on cerebral hypoxia in patients with poor intracranial compliance or increased intracranial pressure [32, 33]. The total incidence of adverse reactions such as nausea, vomiting, dizziness, loss of appetite, restlessness, and respiratory depression in the experimental group was 5.00%, which was significantly lower than 13.00% in the control group, possibly because 0.05 mg/kg midazolam combined with 0.2 μg/kg fentanyl took effect rapidly and had a faster metabolism. The combined application does not cause accumulation in the body, showing good tolerance and high safety.

There are some limitations to the current study. We did not explore oxidative stress levels and pain mediators in the patients, and did not study specific mechanisms nor long-term results. Also, the sample size of this study was small. All these aspects need to be improved in future research.

In conclusion, 0.05 mg/kg midazolam combined with 0.2 μg/kg fentanyl for adult painless bronchoscopy has little effect on SpO_2 index, possesses better sedative effect, reduces the awaking time, and improves adverse reactions. It is worthy of extensive clinical application.

Disclosure of conflict of interest

None.

Address correspondence to: Xianhua Ye, Department of Anesthesiology, The First People's Hospital of Wenling, No. 333, South Chuan'an Road, Taizhou 317500, Zhejiang, P. R. China. Tel: +86-0576-89668222; Fax: +86-0576-89668222; E-mail: yexianhua_@outlook.com

References

[1] Murgu S, Laxmanan B, Stoy S, Egressy K, Chaddha U, Farooqui F, Brunner R, Hogarth K and Chaney M. Evaluation of safety and short-term outcomes of therapeutic rigid bronchoscopy using total intravenous anesthesia and spontaneous assisted ventilation. Respiration 2020; 99: 239-247.

[2] Paul M, Rastogi A, Chatterje A, Agarwal A, Mishra P and Khan A. Comparative evaluation of propofol and combination of propofol-dexmedetomidine in adjunct with topical airway anesthesia for rigid bronchoscopy: a randomized double-blinded prospective study. Ann Card Anaesth 2021; 24: 49-55.

[3] Brady AK, Town JA, Robins L and Bowen J. Bronchoscopy teaching without a gold standard: attending pulmonologists' assessment of learners, supervisory styles, and variation in practice. Chest 2021; 160: 1799-1807.

[4] Murata S, Sasada S, Usui Y, Sakai T, Kirita K, Ishioka K, Takahashi S and Nakamura M. Omission of throat anesthesia using Jackson's spray prior to bronchoscopy for preventing aerosol generation: a survey through patient distress questionnaire. Cureus 2021; 13: e17231.

[5] Kuczynska K and Boncler M. Emerging role of fentanyl in antiplatelet therapy. J Cardiovasc Pharmacol 2020; 76: 267-275.

[6] Gautam G and Khera D. Sedation in pediatric bronchoscopy: propofol versus fentanyl. Indian Pediatr 2020; 57: 483-484.

[7] Trescot AM, Datta S, Lee M and Hansen H. Opioid pharmacology. Pain Physician 2008; 11 Suppl: S133-153.

[8] Egan TD. Are opioids indispensable for general anaesthesia? Br J Anaesth 2019; 122: e127-e135.

[9] Sagiroglu G and Baysal A. Continuous intravenous versus intermittent bolus midazolam with remifentanil during arteriovenous fistula placement with monitored anesthesia care in chronic renal failure patients: a randomized controlled trial. Ann Saudi Med 2020; 40: 175-182.

[10] Doi M, Hirata N, Suzuki T, Morisaki H, Morimatsu H and Sakamoto A. Safety and efficacy of remimazolam in induction and maintenance of general anesthesia in high-risk surgical patients (ASA Class III): results of a multicenter, randomized, double-blind, parallel-

group comparative trial. J Anesth 2020; 34: 491-501.
[11] Dreher M, Ekkernkamp E, Storre JH, Kabitz HJ and Windisch W. Sedation during flexible bronchoscopy in patients with pre-existing respiratory failure: midazolam versus Midazolam plus Alfentanil. Respiration 2010; 79: 307-314.
[12] Barnett AM, Jones R and Simpson G. A survey of bronchoscopy practice in Australia and New Zealand. J Bronchology Interv Pulmonol 2016; 23: 22-28.
[13] Smyth CM and Stead RJ. Survey of flexible fibreoptic bronchoscopy in the United Kingdom. Eur Respir J 2002; 19: 458-463.
[14] Prabhudev AM, Chogtu B and Magazine R. Comparison of midazolam with fentanyl-midazolam combination during flexible bronchoscopy: a randomized, double-blind, placebo-controlled study. Indian J Pharmacol 2017; 49: 304-311.
[15] Rasheed AM, Amirah MF, Abdallah M, P J P, Issa M and Alharthy A. Ramsay sedation scale and richmond agitation sedation scale: a cross-sectional study. Dimens Crit Care Nurs 2019; 38: 90-95.
[16] Maxwell E. Commentary: the effect of using Richmond agitation and sedation scale on hospital stay, ventilator dependence and mortality rate in ICU inpatients: a randomised clinical trial. J Res Nurs 2020; 25: 747-748.
[17] Rashidi M, Molavynejad S, Javadi N, Adineh M, Sharhani A and Poursangbur T. The effect of using Richmond agitation and sedation scale on hospital stay, ventilator dependence, and mortality rate in ICU inpatients: a randomised clinical trial. J Res Nurs 2020; 25: 734-746.
[18] Leiten EO, Eagan TML, Martinsen EMH, Nordeide E, Husebo GR, Knudsen KS, Lehmann S, Svanes Ø, Bakke PS and Nielsen R. Complications and discomfort after research bronchoscopy in the MicroCOPD study. BMJ Open Respir Res 2020; 7: e000449.
[19] Wang N, Jin F, Liu W, Dang S, Wang Y, Yan Y and Wu G. 1% tetracaine hydrochloride injection pure solution aerosol inhalation combined with oral administration of dyclonine hydrochloride mucilage as upper airway anesthesia for bronchoscopy: a randomized controlled trial. Clin Respir J 2020; 14: 132-139.
[20] Madan K, Iyer H, Arunachalam M, Mittal S, Tiwari P, Hadda V, Mohan A and Guleria R. The cricothyroid versus the spray-as-you-go method for topical anesthesia during flexible bronchoscopy: a systematic review and meta-analysis of randomized controlled trials. Lung India 2021; 38: 416-424.
[21] Gibbons AT, Casar Berazaluce AM, Hanke RE, McNinch NL, Person A, Mehlman T, Rubin M and Ponsky TA. Avoiding unnecessary bronchoscopy in children with suspected foreign body aspiration using computed tomography. J Pediatr Surg 2020; 55: 176-181.
[22] Sampsonas F, Kakoullis L, Karampitsakos T, Papaioannou O, Katsaras M, Papachristodoulou E, Kyriakou G, Bellou A and Tzouvelekis A. Bronchoscopy during the COVID-19 pandemic: effect on current practices and strategies to reduce procedure-associated transmission. Expert Rev Respir Med 2021; 15: 773-779.
[23] Chen KZ, Ye M, Hu CB and Shen X. Dexmedetomidine vs remifentanil intravenous anaesthesia and spontaneous ventilation for airway foreign body removal in children. Br J Anaesth 2014; 112: 892-897.
[24] Chaudhary S, Chaudhary S, Kumar M and Salhotra R. Fentanyl versus nalbuphine for intubating conditions during awake fiberoptic bronchoscopy: a randomized double-blind comparative study. J Anaesthesiol Clin Pharmacol 2021; 37: 378-382.
[25] Kumar MP, Patro M, Panigrahy S, Samal S and Kartheek BS. Comparison between intravenous dexmedetomidine and spray as you go with 4% lignocaine versus intravenous fentanyl and transtracheal injection of 4% lignocaine for awake nasotracheal intubation with flexible vedioscope - a randomized single-blind prospective study. Anesth Essays Res 2021; 15: 213-219.
[26] Joskova M, Durdik P, Sutovska M, Grendar M, Koniar D, Hargas L, Banovcin P and Franova S. Negative impact of anesthesia with midazolam, sufentanil, and propofol used in pediatric flexible bronchoscopy on the tracheal ciliary beat frequency in guinea pigs. J Pharmacol Sci 2020; 142: 165-171.
[27] Zhang Q, Zhou J, He Q, Guan S, Qiu H, Xu X, Xu Q, Dai P, Dong D, Wang X and Zhang S. Dexmedetomidine combined with midazolam infusion guided by bispectral index during bronchoscopy. Clin Respir J 2021; 15: 929-936.
[28] Pastis NJ, Yarmus LB, Schippers F, Ostroff R, Chen A, Akulian J, Wahidi M, Shojaee S, Tanner NT, Callahan SP, Feldman G, Lorch DG Jr, Ndukwu I, Pritchett MA and Silvestri GA; PAION Investigators. Safety and efficacy of remimazolam compared with placebo and midazolam for moderate sedation during bronchoscopy. Chest 2019; 155: 137-146.
[29] Matsumoto T, Kaneko A, Fujiki T, Kusakabe Y, Noda A, Tanaka A, Yamamoto N, Tashima M, Tashima N, Ito C, Aihara K, Yamaoka S and Mishima M. Prevalence and characteristics of disinhibition during bronchoscopy with midazolam. Respir Investig 2022; 60: 345-354.
[30] Katsurada M, Tachihara M, Katsurada N, Takata N, Sato H, Mimura C, Yoshioka J, Furukawa

K, Yumura M, Otoshi T, Yasuda Y, Kiriu T, Hazama D, Nagano T, Yamamoto M, Nishimura Y and Kobayashi K. Randomized single-blind comparative study of the midazolam/pethidine combination and midazolam alone during bronchoscopy. BMC Cancer 2022; 22: 539.

[31] Magazine R, Venkatachala SK, Goneppanavar U, Surendra VU, Guddattu V and Chogtu B. Comparison of midazolam and low-dose dexmedetomidine in flexible bronchoscopy: a prospective, randomized, double-blinded study. Indian J Pharmacol 2020; 52: 23-30.

[32] Minami D, Murakami E, Shibata Y, Nakamura K, Kishino T, Takigawa N, Onishi K, Takigawa Y, Shimonishi A, Kudo K, Sato A, Sato K, Fujiwara K and Shibayama T. End-tidal capnographic monitoring during flexible bronchoscopy under fentanyl and midazolam sedation. Ann Palliat Med 2021; 10: 8665-8671.

[33] Sumi T, Kamada K, Sawai T, Shijubou N, Yamada Y, Nakata H, Mori Y and Chiba H. Sedation with fentanyl and midazolam without oropharyngeal anesthesia compared with sedation with pethidine and midazolam with oropharyngeal anesthesia in ultrathin bronchoscopy for peripheral lung lesions. Respir Investig 2021; 59: 228-234.