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Effect of dexmedetomidine and midazolam for flexible fiberoptic bronchoscopy in intensive care unit patients

A retrospective study

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Abstract

This study aimed to investigate the clinical effectiveness of dexmedetomidine and midazolam for sedation of intensive care unit (ICU) patients requiring flexible fiberoptic bronchoscopy (FFB).

This retrospective cohort study included 148 patients from the third ICU ward of the Second Affiliated Hospital of Harbin Medical University (Harbin, China) who received simultaneous invasive mechanical ventilation and FFB between March 2012 and December 2014. Patients were divided into dexmedetomidine (n = 72) and midazolam (n = 76) groups according to sedative mode. The sedative effects, incidence of adverse events, and bronchoscopist satisfaction scores were compared between groups.

During FFB, total sedation time and total time of FFB were significantly shorter in the midazolam group ($P < .001$, respectively), with a lower percentage of these patients requiring propofol for remedial sedation ($P < .001$). The incidence of FFB-related adverse events (including bronchospasm, cough, and decreased oxygen saturation) was significantly higher in dexmedetomidine group compared with midazolam group ($P = .007$, .014 and .008, respectively). However, the incidence of other adverse events was not significantly different between groups. In addition, bronchoscopist satisfaction scores were significantly higher in the midazolam compared with dexmedetomidine group (7.72 ± 1.65 vs 7.08 ± 1.77; $P = .030$).

For sedation of ICU patients during FFB, combination of midazolam and dexmedetomidine demonstrated an enhanced sedative effect, lower incidence of adverse events, and higher bronchoscopist satisfaction score compared with dexmedetomidine alone, thus represents a suitable alternative sedative for FFB patients.

Abbreviations: APACHE = acute physiology and chronic health evaluation, BP = blood pressure, FFB = flexible fiberoptic bronchoscopy, HR = heart rate, ICU = intensive care unit, RASS = Richmond Agitation Sedation Scale, SPO_2 = decreased oxygen saturation.

Keywords: bronchoscopy, deep sedation, dexmedetomidine, midazolam

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YG and KK contributed equally to this work.

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1. Introduction

Flexible fiberoptic bronchoscopy (FFB) is widely used in intensive care unit (ICU) patients and is considered a safe and effective procedure that allows direct airway observation. Although FFB is predominantly used for the diagnosis and treatment of respiratory diseases in critically ill patients,[1,2] the invasive nature of this technology can induce cough, dyspnea, airway reflex contraction, laryngospasm, and catecholamine release, with further detrimental effects on patient prognosis.[3] Consequently, the American College of Chest Physicians has highlighted the necessity of using sedation combined with topical anesthesia during FFB.[4] Appropriate sedation and analgesia during this procedure can improve patient tolerance and comfort, reduce fear, anxiety, and mental stress, and improve overall clinical outcome.[5]

Disease conditions of many ICU patients requiring FFB are often complex, with the majority of patients being on mechanical ventilation. Consequently, these patients are less likely to tolerate FFB stimulation; therefore, deeper sedation is needed to ensure a successful procedure and reduce the risk of adverse events. However, insufficient sedation can induce severe discomfort and further damage in patients.[5]

At present, no guidelines exist for the selection and use of sedatives for FFB.[6] The most commonly used sedatives in clinical practice include dexmedetomidine and midazolam. Previous studies have shown that dexmedetomidine is more effective in conscious and light sedation.[7] Dexmedetomidine can be used for long-term sedation during mechanical ventilation in critically ill patients, which can reduce the ventilation time and ICU stay.[8,9] Furthermore, dexmedetomidine can provide appropriate anesthesia depth and ideal conditions for rigid bronchoscopic airway removal of foreign bodies in children.[10] However, there are no studies to date that have compared the sedative effects and adverse reactions of different sedatives during FFB in critically ill ICU patients on mechanical ventilation. In the present study, the clinical effectiveness of dexmedetomidine and midazolam for sedation of ICU patients before FFB was compared.

2. Materials and methods

2.1. Study design

The present study is a retrospective cohort study.

2.2. Study population

Patient inclusion criteria included: ICU patients receiving invasive mechanical ventilation and requiring FFB in the third ICU ward of the Second Affiliated Hospital of Harbin Medical University between March 2012 and December 2014; aged >18 years; and stable hemodynamics. Patient exclusion criteria included: hypoxemia; left ventricular ejection fraction <0.30, heart rate (HR) <50 beats/min, grade II–III cardiac conduction block, or pathologic sinus sick syndrome; unstable angina pectoris or acute myocardial infarction; Glasgow Coma Scale score ≤8; loss of hearing; combined severe complications such as diabetic ketoacidosis, liver failure, renal failure, and so on; neuromuscular transmission failure; women in gestation or breastfeeding; blood purification treatment; psychological diseases, or long-term use or addiction to antipsychotics; long-term use of sedative drugs; and allergy to the sedatives or analgesics used in the study. Written informed consent was obtained from all patient families before carrying out FFB. Patients were divided into 2 groups according to the sedatives used.

2.3. Sedation and analgesia

2.3.1. Drug selection. Fentanyl citrate injection (2 mL [0.1 mg]/ampoule, Renfu Pharmaceutical Co., Ltd., Yichang) was used as the analgesia. The following drugs were used for sedation: dexmedetomidine hydrochloride injection (2 mL [200 μg]/ampoule, Hengrui Pharmaceutical Co., Ltd, Jiangsu; period of validity: 18 months); midazolam injection (2 mL [10 mg]/ampoule, Enhua Pharmaceutical Co., Ltd; period of validity: 36 months); and propofol injection (50 mL [1 g]/ampoule, Fresenius Kabipharmaceutical Co., Ltd, Beijing; period of validity: 36 months).

2.3.2. Drug administration. All drugs were administered after recovery of the patients' conscious or reaching 0 score of the Richmond Agitation Sedation Scale (RASS). Endoscopic dripping of 2% lidocaine (3–5 mg/kg) was used for topical anesthesia, and then intravenous injection of fentanyl citrate (2.0 μg/kg) was administered. Dexmedetomidine hydrochloride injection with a loading dose of 0.8 μg/kg was used for intravenous pumping for 10 minutes, after which the dose was switched to 0.2 to 0.7 μg/kg/h for maintenance. Midazolam injection with a loading dose of 0.05 mg/kg was used for intravenous pumping for 10 minutes, after which the dose was switched to 0.02 to 0.2 mg/kg/h for maintenance. RASS score was obtained every 5 minutes, and the drug dose was adjusted accordingly until it reached a satisfactory deep sedation level with an RASS score of −3 to −4. Propofol injection with a loading dose of 2.0 mg/kg could also be used for intravenous injection and switched to 0.5 to 4 mg/kg/h for remedial sedation if necessary. After completion of FFB, further sedation and analgesia could be continued after the patient's conditions were evaluated. For patients with severe adverse reactions during FFB, the procedure was discontinued and symptomatic treatment was provided. The disease conditions were then evaluated to determine whether the procedure could be continued.

2.4. Invasive mechanical ventilation

All patients received electrocardiogram monitoring, invasive artery blood pressure (BP) monitoring, and decreased oxygen saturation (SpO_2) monitoring (Mindray monitoring device, BeneView T8). Ventilator parameters were set to maintain the SpO_2 >90% during FFB, otherwise examinations were discontinued.

2.5. Fiberoptic bronchoscopy

A fiberoptic bronchoscope (Olympus LF-TP, Japan) was used in accordance with standardized procedures.

2.6. Data collection

2.6.1. Baseline data. Sex, age, height, weight, acute physiology and chronic health evaluation (APACHE) II score, and indications for FFB were obtained from patient medical records.

2.6.2. Sedative effects. Total sedation time, time of bedside FFB, frequencies of remedial sedation by propofol, and incidence of adverse events (including cough, nausea, and bronchospasm) were collected. – (HR), BP, respiration rate, and SpO_2 were recorded every five minutes.

2.6.3. Bronchoscopist satisfaction scores. After completion of FFB, bronchoscopist sedation satisfaction scores were recorded for all patients ("0" indicated very unsatisfied and "10" indicated very satisfied).

2.7. Statistical analyses

SPSS 22.0 (SPSS Inc, Chicago, IL) and SAS 9.1 (SAS Institute, Cary, NC) software were used for statistical analysis. Quantitative data are shown as means ± standard deviations and qualitative data are shown as percentages. The Student t test and Mann-Whitney U test were used to compare quantitative data between groups, whereas the χ^2 test was used to compare qualitative data between groups. $P < .05$ was considered to be statistically significant.

3. Results

3.1. Patient baseline data

There were no significant differences in patient baseline data between groups ($P > .05$, Table 1).

Table 1

Patient baseline data.

Parameter	Dexmedetomidine group (n = 72)	Midazolam group (N = 76)	P
Sex male (%)	42 (58.3)	37 (48.7)	.240
Age, y	58.03 ± 10.47	59.25 ± 11.54	.367
Height, cm	167.64 ± 8.53	169.17 ± 8.89	.710
Weight, kg	67.68 ± 8.62	66.32 ± 9.94	.232
APACHEII score	17.54 ± 4.62	16.75 ± 4.44	.219
Indications for fiberoptic bronchoscopy			
Examination diagnosis (%)	21 (29.2)	27 (35.5)	.409
Bronchoalveolar lavage (%)	51 (70.8)	49 (64.5)	

APACHE II = acute physiology and chronic health evaluation II.

3.2. Sedative effects

As shown in Table 2, total sedation time and time of bedside FFB were significantly shorter in the midazolam group compared with the dexmedetomidine group ($P < .001$, respectively). The frequency and percentage of patients that used propofol for remedial sedation were significantly higher in the dexmedetomidine group compared with the midazolam group ($P < .001$). The incidence of FFB-related adverse events (including bronchospasm, cough, and decreased SpO_2) was significantly higher in the dexmedetomidine group compared with the midazolam group ($P = .007$, .014, 0.008, respectively, Table 3). When assessed individually, the incidence of decreased SpO_2 was significantly higher in the dexmedetomidine group compared with the midazolam group ($P = .008$); however, the incidence of other adverse events was not significantly different between groups (Table 4).

3.3. Bronchoscopist satisfaction score

After completion of FFB, the mean bronchoscopist satisfaction scores were 7.08 ± 1.77 and 7.72 ± 1.65 in the dexmedetomidine and midazolam groups, respectively ($P = .030$, Table 2).

4. Discussion

FFB can cause cough, shortness of breath, and irritation of the nose and throat, which in turn can stimulate the release of catecholamine, leading to tachycardia, vasoconstriction, and myocardial ischemia in patients with impaired cardiopulmonary function.[3] In short, the influence of this technique in ICU patients can ultimately lead to worse respiratory cycle.[11] FFB is more invasive and painful than other techniques; sedation can reduce patient anxiety and pain, and enhance comfort, thus reducing further serious injury.[5]

Table 2

Sedative effects during fiberoptic bronchoscopy.

Parameter	Dexmedetomidine group (n = 72)	Midazolam group (n = 76)	P
Sedation parameter			
Frequency of remedial sedation by propofol (%)	52 (72.2)	22 (28.9)	<.001
Total sedation time, min	27.85 ± 3.96	23.04 ± 3.45	<.001
Time of bedside FFB, min	20.07 ± 3.52	16.97 ± 3.43	<.001
Satisfaction score of the bronchoscopists	7.08 ± 1.77	7.72 ± 1.65	.030

FFB = flexible fiberoptic bronchoscopy.

Table 3

Incidence of fiberoptic bronchoscopy-related adverse events.

Parameter	Dexmedetomidine group (n = 72)	Midazolam group (n = 76)	P
Cough	41 (56.9)	28 (36.8)	.014
Nausea	12 (16.7)	13 (17.1)	.943
Bronchospasm	49 (68.1)	35 (46.1)	.007
Tachycardia	21 (29.2)	25 (32.9)	.624
Arrhythmia	5 (6.9)	6 (7.9)	.826
SpO_2 decrease	32 (44.4)	18 (23.7)	.008
Hypertension	11 (15.3)	12 (15.8)	.932
Others	4 (5.6)	6 (7.9)	.571

SPO_2 = decreased oxygen saturation.

Although FFB is invasive, it lacks standardization, particularly with respect to sedative selection and application, resulting in vast clinical differences.[12,13] Each sedative has its own advantages and disadvantages when applied in clinic. For ICU patients requiring bedside FFB, identifying an optimal sedation and analgesia strategy with good sedative effect, low risk of adverse events, high bronchoscopist satisfaction score, and high operability is important. Very few studies have addressed this clinical issue; therefore, the present study compared the clinical effectiveness and safety profile of 2 commonly used sedatives during FFB.

Before FFB, all analgesic and sedative drugs were discontinued until recovery of the patients' conscious or reaching 0 score of the RASS. All patients received 2% lidocaine (3–5 mg/kg) as a topical anesthesia to reduce the incidence of coughing and the required dose of intravenous sedative.[14] Fentanyl citrate, a synthesized phenyl piperidine drug, was also administered to all patients. This narcotic analgesic drug is commonly used in clinical practice because it has a relatively weak respiratory inhibition effect and can inhibit stress reactions of the cardiovascular system. During FFB of ICU patients, common intravenous sedatives include propofol, dexmedetomidine, and midazolam. Propofol is a short-acting intravenous sedation drug that elicits sedation, hypnosis, and amnesia effects. The advantages of propofol include its fast-acting and -elimination properties, as well as its promotion of laryngeal reflex inhibition and bronchial smooth muscle dilation.[15] The disadvantages of propofol include transient dose-dependent respiration and circulation inhibition,[16] and an elevated risk of delirium.[17]

Dexmedetomidine is a new α_2 adrenergic receptor agonist with high efficiency and selectivity which can bind to the α_2 receptor in brain and spinal cord, reduce the plasma concentration of catecholamine,[18] and exert sedative, anti-anxiety and analgesic

Table 4

Incidence of drug-related adverse events.

Parameter	Dexmedetomidine group (n = 72)	Midazolam group (n = 76)	P
Nausea	12 (16.7)	13 (17.1)	.943
Tachycardia	21 (29.2)	25 (32.9)	.624
Bradycardia	7 (9.7)	5 (6.9)	.614
Arrhythmia	5 (6.9)	6 (7.9)	.826
SpO_2 decrease	32 (44.4)	18 (25.0)	.008
Hypotension	8 (11.1)	10 (13.2)	.681
Hypertension	11 (15.3)	12 (15.8)	.932
Others	4 (5.6)	6 (7.9)	.571

SPO_2 = decreased oxygen saturation.

effects.[19] Additionally, this drug has an anti-sialic effect and can induce retrograde amnesia[20] and reduce the incidence of delirium.[21] Dexmedetomidine activates the α_2 adrenergic receptor at the pre- and postsynaptic membranes of ganglions in the brain and spinal cord, which would in turn inhibit sympathetic nerve excitement, enhance vagal nerve activity, and induce bradycardia, thus decreasing BP.[22] Midazolam is a fast-acting sedative drug, which can also induce hypnosis, anti-anxiety, and retrograde amnesia, with dose-dependent effects on the respiratory and circulatory systems. However, when used in patients with liver and/or renal dysfunction, the risks of drug accumulation[23] and delirium[24] are relatively high.[25]

During FFB, intravenous injection of dexmedetomidine can not only prevent the bronchial constriction induced by the release of histamine, and reduce airway responsiveness,[26] but can also inhibit excitement of the sympathetic nervous system,[27,28] maintain stress response hormones at low-level during the procedure,[29] and enhance the comfort and compliance of patients.

The effect of dexmedetomide in conscious sedation and maintaining light sedation is more pronounced and can be applied to critically ill patients, but the effect in medium-to-depth sedation is unknown.[30] Moderate sedatives have been increasingly used to improve patient comfort during flexible bronchoscopy (FB).

However, the findings of the present study showed that the sedative effects, incidence of adverse events, and bronchoscopist satisfaction scores were superior in midazolam group compared with dexmedetomidine group. In addition, the use of dexmedetomidine alone did not provide a sufficient sedative effect, which could be associated with the following factors. First, all patients were critically ill and on mechanical ventilation, therefore were less likely to tolerate FFB stimuli, thus a deeper sedation target (RASS score of −3 to −4) was needed to eliminate adverse stimulations. However, an advantage of dexmedetomidine is that it provides conscious and light sedation,[31] thus improving its clinical[32,33] and economic[34] values.

In the present study, the dexmedetomidine dose did not reach the target depth of sedation; therefore, the percentage of propofol usage for remedial sedation was higher, which is in agreement with results reported by Lee et al.[35] Second, the FFB stimulation intensity was underestimated by the majority of clinicians. Third, because the patients did not reach the sedation target rapidly and maintain sedation depth, the incidence of adverse events was significantly higher in the dexmedetomidine group compared with the midazolam group. This prolonged the total sedation time and time of bedside FFB, reduced the bronchoscopist satisfaction scores, and evidently increased the frequency of using propofol for remedial sedation. Although increasing the dose of dexmedetomidine might result in some improvements, the risk of adverse events could also increase, which could be fatal. Finally, although the percentage use of propofol for remedial sedation was significantly higher in the dexmedetomidine group, the incidence of cardiovascular system-related adverse events was not increased compared with the midazolam group. However, the combined use of dexmedetomidine and propofol could inevitably increase the risk of respiratory inhibition, which could be one cause of decreased SpO_2.

There were several limitations in the present study. First, patients were selected from a single center making the level of evidence for this retrospective study low; further prospective studies are needed to verify the outcome of our study. Second, FFB was performed by different bronchoscopists; therefore, the results could be affected by operator experience and proficiency. Third, the complications that arose in the study may have been because of both the FFB procedure and the drug type used, which may affect overall patient judgment. Finally, the eligibility criteria were very strict, with many exclusion criteria applied; consequently, the sample size was relatively small. Future studies comprising larger sample sizes are needed to verify our findings.

5. Conclusions

In summary, the present study shows that when used alone, dexmedetomidine is suitable for conscious sedation and maintaining light sedation. However, for invasive procedures requiring relatively high stimulations, drug combinations could help maintain sufficient sedative depth and bronchoscopist satisfaction score, reduce adverse reactions, and thus improve patient comfort and safety. And this may provide insight and help for better sedation and clinical outcomes.

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