

Analgo-sedation during flexible fiberoptic bronchoscopy: Comparing the clinical effectiveness and safety of remifentanil versus midazolam/propofol

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Abstract

Background: There are limited data regarding the efficacy and safety of remifentanil sedation for diagnostic bronchoscopy. The aim of this study was to evaluate the clinical efficacy and safety of remifentanil by comparing it with those of the conventional drugs, midazolam and propofol. **Methods:** A retrospective study of 186 patients who underwent diagnostic bronchoscopy at Chonbuk National University Hospital was performed. Patients were classified into the remifentanil group and midazolam/propofol group according to the drugs used during bronchoscopy. **Results:** Of the 186 patients, 111 patients received remifentanil and 75 received midazolam/propofol during the bronchoscopy. The proportion of patients who required bronchoscopy for endobronchial inspection alone was significantly higher in the midazolam/propofol group than in the remifentanil group (93.3% vs. 71.2%; $p < 0.001$). In contrast, the proportion of patients who required more invasive procedures, such as bronchoscopic biopsy, bronchoalveolar lavage, or transbronchial lung biopsy, was significantly higher in the remifentanil group than in the midazolam/propofol group (27.8% vs. 6.7%; $p < 0.001$). The recovery time was significantly shorter in the remifentanil group than in the midazolam/propofol group (mean 6.4 min vs. 11.6 min, $p < 0.001$). There was no significant difference between the groups with regard to safety events including desaturation, hypotension, and arrhythmia. **Conclusions:** Despite the higher proportion of patients who underwent more invasive procedures in the remifentanil group than in the midazolam/propofol group, there was no significant difference in safety events between the groups. Those in the remifentanil group also demonstrated a faster recovery time than those in the midazolam/propofol group.

Background

Flexible bronchoscopy remains the gold standard for numerous diagnostic and therapeutic interventions and has become an integral part of pulmonary medicine [1]. Given its widespread use, it is important to select appropriate sedation to relieve the anxiety and pain of patients undergoing bronchoscopy [2-4]. The type of sedation may also be helpful for the bronchoscopist to facilitate the procedure [4].

Although the current guidelines recommend the combined use of an opioid and midazolam for bronchoscopy sedation [3], physicians often use a single drug, or a combination of benzodiazepines, propofol, and opioids in this setting [5, 6]. In addition, with the development of new drugs, remifentanil and dexmedetomidine have been introduced as options for analgosedation for flexible bronchoscopy in adults [7-11]. Accordingly, the combination of new drugs and conventional drugs has enabled a wide variety of combinations of drugs to be used for analgosedation for flexible bronchoscopy. Several studies have demonstrated the safety and efficacy of the addition of remifentanil or dexmedetomidine (to conventional drugs) in adult patients who underwent flexible bronchoscopy [7-10]. However, the best-standardized practice for the use of sedation during bronchoscopy has yet to be determined.

Remifentanil is an ultra short-acting new opioid analgesic drug which is commonly used to relieve pain during the surgery and as adjunctive to an anesthetic [12]. The ultrafast offset and short half-life also

make it an ideal drug for analgosedation in ICU patients [13]. Considering that remifentanyl has excellent analgosedation effects with an advantage of the short half-life, remifentanyl could become an alternative to conventional treatments (including the combination of a benzodiazepine and propofol) for sedation in bronchoscopy. However, few studies have compared the effectiveness and safety profile of remifentanyl versus a combination of midazolam and propofol. Therefore, the aim of this study was to compare the effectiveness and safety of analgosedation using remifentanyl versus the combination of midazolam and propofol during flexible bronchoscopy.

Methods

Study design and population

This retrospective observational study was conducted at a tertiary university-affiliated hospital from May 2015 to September 2017. It was approved by the local Institutional Review Board (IRB no. CUH 2019-05-083). The patients were stratified into the remifentanyl group and midazolam/propofol group according to the drugs used during flexible bronchoscopy.

Flexible bronchoscopy

Flexible fiberoptic bronchoscopy was performed with standard fiberscopes by two professional pulmonologists. A flexible bronchoscope (BF-F260, BF-6C260, 1T260, BF-Q290, 1TQ290, Olympus, Tokyo, Japan) was inserted via the nasal approach with subjects in the supine position.

All consecutive patients who were spontaneously breathing were eligible. All patients had fasted for at least eight hours prior to the start of the procedure and had an intravenous catheter. Topical anesthesia was performed using 4% lidocaine spray in the oral cavity. While the vocal cords and carina were visualized, 4 ml of 2% lidocaine was delivered through the bronchoscope channel to suppress cough. Additional topical anesthesia was applied to the major bronchi as needed (at the bronchoscopists' discretion) for a maximum total lidocaine dose of 7 mg/kg.

Sedation

Midazolam/propofol group

Pretreatment with 1-2 mg midazolam (Midazolam[®], Bukwang, Seoul, Republic of Korea) was used to relieve significant preprocedural anxiety. Patients were treated with an additional 1mg of midazolam if necessary. Next, propofol (Anepol[®], Hana Pharmaceutical Co., Seoul, Republic of Korea) was administered according to our hospital's protocol (Table 1).

Remifentanil group

Patients received no premedication in the remifentanil group. Remifentanil (Ultiva[®], GlaxoSmithKline, Seoul, Republic of Korea) was initially administered with a bolus dose of the study drug (0.5-1 mcg/kg), followed by a 0.02–0.04mcg/kg/min continuous infusion at the discretion of the bronchoscopist. A bolus dose of the study drug in proportional volumes was administered slowly (over a period of 60 s) to minimize known adverse effects, such as respiratory depression, hypotension, and bradycardia. The fibroscope was inserted into the patient 3-5 minutes after the remifentanil initial onset time. The remifentanil infusion was immediately stopped if bradypnea/apnea or hemodynamic collapse occurred.

Outcome variables

The primary outcomes included the incidences of oxygen desaturation and oxygen saturation trend between the two groups. Oxygen desaturation was defined as an oxygen saturation < 90% for more than 10s. In the event of oxygen desaturation, oxygen delivery was increased from 4 to 10 liter/min. Additional assistance (including reservoir bag mask, high flow nasal cannula, and intubation followed by bag valve mask ventilation) was performed in a stepwise manner as needed.

Secondary outcomes included hemodynamic variables, the incidence of hemodynamic adverse events, patient satisfaction scores, level of sedation (MOAA/S score), and recovery time (Modified Aldrete score).

Vital signs were continuously monitored before, during, and after the procedure by the bronchoscopist and nurses. Bradycardia (defined by a heart rate < 60 beats/min or a decrease of >15 beats/min from baseline) was treated with intravenous atropine 0.5 mg. Hypotension (defined by a systolic blood pressure <90 mm Hg or a decrease of >20 mmHg from baseline) was treated with intravenous epinephrine 5 mg. Bradypnea (defined by a respiratory rate <12/min or apnea >10s), and other adverse reactions were noted throughout the procedure.

Immediately after the procedure, the patients and bronchoscopists were asked about their level of satisfaction with the procedure (with regard to recall, pain, and discomfort for patients, and ease of the procedure). Patients were also asked if they would be willing to undergo repeat bronchoscopy if needed. This response was recorded as 'yes' or 'no'.

Levels of sedation were evaluated at the initiation of the procedure and 5 min after the procedure began using the modified observer's assessment of alertness/sedation/(MOAA/S) scale [14]. Recovery time was classified as fast and delayed according to the median value of recovery time.

Statistical analysis

Continuous variables are presented as means (SD) or medians (interquartile range, [IQR]). Categorical variables are presented as counts (%). Continuous variables were compared using the Mann-Whitney U test or T-test for continuous variables. Categorical variables were compared using the chi-square test or Fischer's exact test, as appropriate. In order to evaluate the factors associated with fast recovery time, we performed univariable and multivariable logistic regression analyses. The following factors were included in the multivariable model: age, sex, body mass index, chronic obstructive pulmonary disease or asthma, chronic heart disease, bronchoscopy indication, procedure purpose, and type of sedative drugs. Two-sided p values < 0.05 were considered significant. All statistical analyses were performed using R (ver. 3.2.3; R Foundation for Statistical Computing, Vienna, Austria) and STATA version 15 (StataCorp LP, College Station, TX, USA).

Results

Patients

The baseline characteristics are summarized in Table 1. There were no significant differences between the two groups with regard to age, sex, body mass index, comorbidities such as hypertension, diabetes mellitus, asthma, chronic obstructive pulmonary disease, and chronic heart disease, or pulmonary function.

Indication for bronchoscopy and use of sedative drugs

Infection, lung cancer, and hemoptysis were the most common indications of bronchoscopy (Table 2). Patients in the remifentanil group were more likely to undergo invasive procedures during the bronchoscopy (beyond inspection alone) than were those in the midazolam/propofol group. The median procedure time was 9.0 min (IQR, 8.0-10.0 min) in the remifentanil group vs. 11.0 (IQR, 10-13 min) in the midazolam/propofol group ($p < 0.001$). The remifentanil group received a median of 0.2 ug/kg/min (IQR, 0.18-0.33 ug/kg/min) of remifentanil. The midazolam/propofol group received a median of 1 mg of midazolam (IQR, 0-4 mg) and 83.0 ug/kg/min (66.0-100.0 ug/kg/min) of propofol.

Comparing the adverse events and recovery time between groups

There were no significant differences in oxygen desaturation, lowest peripheral capillary oxygen saturation, heart rate, antidote use, or sedation discontinuation between the remifentanil group and midazolam/propofol group. However, hypertension, defined by a blood pressure $>150/90$ mmHg was significantly more common in the remifentanil group than it was in the propofol/midazolam group

(52.3% vs. 30.7%; $p = 0.008$). In contrast, the recovery time was significantly lower in the remifentanil group than in the midazolam/propofol group (mean \pm SD, 6.4 ± 3.0 min vs. 11.6 ± 4.0 min, $p < 0.001$) (Table 3).

The relationship between remifentanil use and recovery time

In both univariable and multivariable analyses, the use of remifentanil was associated with more rapid recovery than was the use of midazolam/propofol (unadjusted OR = 7.70, 95% CI = 2.74-21.65; adjusted OR = 15.88, 95% CI = 4.14-60.90) (Table 4).

Discussion

We evaluated 186 subjects who underwent flexible bronchoscopy under sedation. Approximately 60% of these patients received remifentanil, while the remaining 40% received a combination of midazolam and propofol for procedural sedation. The patients in the remifentanil group were more likely to undergo invasive procedures during bronchoscopy (such as bronchoscopic biopsy, bronchoalveolar lavage, or transbronchial lung biopsy) than those in the midazolam/propofol group. Despite this finding, there was no significant difference between the groups in the occurrence of adverse safety events, including oxygen desaturation, hypotension, and arrhythmia. In addition, the recovery time was significantly shorter in the remifentanil group than in the midazolam/propofol group.

Flexible bronchoscopy is an endoscopic procedure during which an optical instrument is placed inside the airways to visualize the tracheobronchial tree. The value of bronchoscopy has grown in both diagnostic and therapeutic capacities. Moderate sedation, in which the patient is able to maintain his/her airway patency and cardiorespiratory function during the procedure (but does not experience undue pain/anxiety), is necessary to perform bronchoscopy in a safe and effective way. In this setting, sedation is not administered by an anesthesiologist, but instead by the bronchoscopist. The bronchoscopist, therefore, is ultimately responsible for the patient's wellbeing. Therefore, it is very important that the bronchoscopist administers appropriate pharmacological sedatives to achieve an appropriate level of consciousness to perform the procedure.

Ideal drugs for procedural sedation and analgesia (PSA), or "conscious sedation," have a rapid onset and short duration of action, and maintain hemodynamic stability with no major side effects [15]. The classically used sedative drugs include the single or combined use of benzodiazepines, propofol, and opioids. A 2003 United Kingdom survey found that 78% of bronchoscopists routinely use midazolam sedation alone and that midazolam plus fentanyl/alfentanil was the most frequently combined regimen [16]. Another study found that the most commonly used drugs in Switzerland were midazolam (46%) and propofol (77%) [17]. However, unfortunately, there are no clear recommendations favoring one sedation

regimen over another. The introduction of new sedative drugs, such as remifentanyl and dexmedetomidine, has added to the complexity of combining sedative regimens [7-11].

Analgo-sedation refers to the use of an analgesic drug (usually an opioid) before a sedative is used to reach the sedative goal [18]. Analgo-sedation is preferred over the sedative-hypnotic approach in critically ill patients, for whom the primary goal is to address pain and discomfort before adding hypnotic agents [18]. The use of analgo-sedation has increased substantially over time and is accepted as a common protocol in the management of intensive care unit (ICU) patients in many hospitals [18]. Accumulating data have suggested that analgo-sedation is safe and effective for the management of very vulnerable ICU patients. Although these data also suggest that analgo-sedation is safe for use during fiberoptic bronchoscopy, there is little evidence supporting this practice.

Remifentanyl is a potent, selective μ -opioid receptor agonist that is metabolized by blood and tissue esterases independent of organ function [19]. Remifentanyl has a rapid onset and a short duration of action (half-life < 10 min) with no tissue accumulation. The advantage of this drug is that its effect does not last long after it is stopped. Therefore, remifentanyl has been preferably used and has been shown to be of benefit in vulnerable patient populations, such as ICU patients [9, 10] and infants and children [20, 21].

Interestingly, despite several advantages of remifentanyl, its utility for PSA in patients undergoing fiberoptic bronchoscopy has not been well elucidated. Two studies showed that the use of remifentanyl alone is safe in ICU patients [9, 10]. However, most other studies regarding remifentanyl studied its use in combination with other drugs [7, 20, 21]. For example, Ryu and colleagues showed that the use of remifentanyl plus propofol was associated with a shorter recovery time than was that of dexmedetomidine. However, the combination of remifentanyl and propofol during bronchoscopy led to a higher incidence of desaturation and need for oral cavity suctioning than did dexmedetomidine use [7]. Therefore, it is unclear whether remifentanyl can be safely and effectively used alone for PSA during fiberoptic bronchoscopy. From this perspective, our study provides important evidence that remifentanyl can be used alone for PSA during fiberoptic bronchoscopy including cases that require complex procedures. In addition, we found that remifentanyl use was associated with faster recovery time and comparable adverse events to those of midazolam/propofol use.

One strength of our study is that it raises important questions regarding the clinical usefulness of remifentanyl use alone for analgo-sedation during fiberoptic bronchoscopy. To the best of our knowledge, this is the first study to comprehensively evaluate the clinical utility and safety of remifentanyl use in fiberoptic bronchoscopy in comparison with those of midazolam/propofol. Another strength of our study is that we employed a larger study population than did prior studies that evaluated the use of remifentanyl alone during fiberoptic bronchoscopy. Regardless, this study also has several limitations. First, it has an inherent bias due to its retrospective design. It was also performed in a single university hospital. Another limitation is that the analgo-sedation drugs used in each patient were chosen at the discretion of the attending physicians. Therefore, this discretion may have resulted in the more frequent use of

remifentanil (over conventional drugs) in vulnerable patients or in those who required more complex procedures. Therefore, the remifentanil group was more prone to include patients with disadvantageous clinical characteristics than was the midazolam/propofol group. Despite this limitation, we found that there were no significant differences between the groups with regard to adverse events.

Conclusions

Despite a higher proportion of patients who underwent more invasive procedures in the remifentanil group than in the midazolam/propofol group, there was no significant difference in the occurrence of safety events between the groups. Furthermore, the recovery time was faster in the remifentanil group than it was in the midazolam/propofol group. Our findings suggest that remifentanil alone can be safely and effectively used for PSA during fiberoptic bronchoscopy regardless of the clinical indications.

Abbreviations

CI: confidence interval; ICU: intensive care unit; IQR: interquartile range; PSA: procedural sedation and analgesia; SD: standard deviation

Declarations

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Availability of data and materials

All data extracted in this study are included in this article.

Authors' contributions

Conception and design: H.L., Y.H.C., S.Y.P.; Data analysis: H.L., S.Y.P.; Data interpretation and manuscript writing: H.L., Y.H.C., S.Y.P.; Revision of the manuscript and contribution to intellectual content: H.L., Y.H.C., S.Y.P.; S.Y.P. is the guarantor of the manuscript.

Ethical approval and consent to participate

The study protocol has been approved by the Institutional Review Board of Chonbuk National University Hospital (CUH 2019-05-083). Given the retrospective nature of the study and the use of anonymized patient data, the requirement for informed consent was waived.

Consent for publication

Not applicable.

Competing interest

None to disclose.

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Tables

Table 1. Baseline characteristics

| | Remifentanyl group (n = 111) | Propofol / Midazolam group (n = 75) | p |
|---------------------------------------|---------------------------------|-------------------------------------|-------|
| Age, years | 59.0 (51.0-70.5) | 58.0 (42.0-71.5) | 0.158 |
| Sex, male | 51 (45.9) | 29 (38.7) | 0.405 |
| Body mass index, kg/m ² | 22.0 (20.0-24.0) | 22.0 (20.0-24.5) | 0.630 |
| Comorbidities | | | |
| Hypertension | 33 (29.7) | 17 (22.7) | 0.370 |
| Diabetes mellitus | 12 (10.8) | 4 (5.3) | 0.298 |
| Asthma | 1 (0.9) | 2 (2.7) | 0.730 |
| Chronic obstructive pulmonary disease | 2 (1.8) | 2 (2.7) | 1.000 |
| Chronic heart disease | 6 (5.4) | 4 (5.3) | 1.000 |
| Pulmonary function | | | |
| FVC, L | 94.0 (85.0-102.0) | 99.0 (88.5-107.5) | 0.076 |
| FVC % predicted | 2.9 (2.4-3.5) | 3.1 (2.6-3.7) | 0.129 |
| FEV1, L | 99.0 (90.0-111.0) | 102.5 (91.0-111.0) | 0.691 |
| FEV1 % predicted | 2.3 (1.8-2.7) | 2.4 (1.9-2.8) | 0.538 |
| FEV1/FVC | 78.0 (73.0-82.5) | 76.0 (71.0-82.5) | 0.726 |

Data are present as number (%) or median (interquartile range).

FVC, forced expiratory volume; FEV1, forced expiratory volume in 1 second.

14

Table 2. Indication for bronchoscopy and the use of sedative drugs

| | Remifentanil group (n = 111) | Propofol / Midazolam group (n = 75) | p |
|--|---------------------------------|--|---------|
| Indication for bronchoscopy | | | 0.137 |
| Lung cancer | 19 (17.1) | 6 (8.0) | |
| Infection | 45 (40.5) | 40 (53.3) | |
| Hemoptysis | 13 (11.7) | 12 (16.0) | |
| Interstitial lung disease | 2 (1.8) | 0 (0) | |
| Other | 32 (28.8) | 17 (22.7) | |
| Procedure | | | 0.005 |
| Endobronchial inspection only | 81 (73.0) | 70 (93.3) | |
| Endobronchial inspection with bronchoscopic biopsy | 20 (18.0) | 1 (1.3) | |
| Endobronchial inspection with BAL and TBLB | 2 (1.8) | 0 (0.0) | |
| Endobronchial inspection with BAL | 8 (7.2) | 4 (5.3) | |
| Procedure duration, min | 9 (8-10) | 11 (10-13) | < 0.001 |
| Sedative drugs | | | |
| Midazolam dose, mg | - | 2 (0-4) | |
| Propofol dose rate, ug/kg/min | - | 83.0 (66.0-100.0) | |
| Remifentanil dose rate, ug/kg/min | 0.2 (0.18-0.33) | | |

Data are present as number (%) or median (interquartile range).

BAL, bronchoalveolar lavage; TBLB, transbronchial lung biopsy.

Table 3. Comparing adverse events and recovery time across groups

| | Remifentanil group (n = 111) | midazolam/propofol group (n = 75) | <i>p</i> |
|--------------------------|---------------------------------|--------------------------------------|----------|
| Desaturation | 9 (8.1) | 6 (8.0) | 1.000 |
| Lowest SpO ₂ | 73.2 ± 12.3 | 81.8 ± 6.0 | 0.174 |
| Heart rate | | | 0.294 |
| Tachycardia | 18 (16.2) | 17 (22.7) | |
| Bradycardia | 5 (4.5) | 1 (1.3) | |
| Blood pressure | | | 0.008 |
| Highest BP > 150/90 mmHg | 58 (52.3) | 23 (30.7) | |
| Lowest BP < 90/60 mmHg | 0 (0) | 1 (1.3) | |
| Recovery time, min | 6.4 ± 3.0 | 11.6 ± 4.0 | < 0.001 |
| Antidote use | 2 (1.8) | 1 (1.3) | 1.0 |
| Discontinuation | 7 (6.3) | 5 (6.7) | 1.0 |

Data are present as number (%) or mean (standard deviation).

Tachycardia and bradycardia were defined as HR > 100/min and HR < 60/min, respectively.

SpO₂, peripheral capillary oxygen saturation

Table 4. Factors associated with rapid recovery in patients undergoing sedative bronchoscopy

| | Univariable analysis | | Multivariable analysis | |
|--------------------------------------|------------------------|---------|------------------------|---------|
| | Unadjusted OR (95% CI) | P value | adjusted OR (95% CI) | P value |
| Age, yr | 0.98 (0.95-1.01) | 0.131 | 0.97 (0.93-1.001) | 0.059 |
| Female | 0.71 (0.30-1.71) | 0.448 | 0.53 (0.18-1.54) | 0.241 |
| Body mass index, kg/m ² | 0.93 (0.93-1.11) | 0.772 | 0.92 (0.82-1.04) | 0.195 |
| COPD or asthma | 0.37 (0.07-2.01) | 0.249 | 0.93(0.11-7.76) | 0.946 |
| Chronic heart disease | 2.74 (0.76-9.91) | 0.123 | 0.62 (0.09-4.32) | 0.628 |
| Indication | | | | |
| Other | Ref | | Ref | |
| Lung cancer | 0.53 (0.15-1.95) | 0.343 | 0.69 (0.13-3.66) | 0.665 |
| Infection | 0.90 (0.31-2.59) | 0.841 | 1.43 (0.40-5.05) | 0.581 |
| Interstitial lung disease | 0.98 (0.22-4.28) | 0.976 | 1.72 (0.29-10.06) | 0.548 |
| Procedure | | | | |
| Inspection only | Ref | | Ref | |
| Inspection with bronchoscopic biopsy | 0.92 (0.25-3.39) | 0.896 | 0.27 (0.04-1.64) | 0.154 |
| Inspection with BAL and/or TBLB | 0.92 (0.19-4.40) | 0.913 | 0.67 (0.10-4.55) | 0.684 |
| Sedative drug | | | | |
| Midazolam/propofol | Ref | | Ref | |
| Remifentanyl | 7.70 (2.74-21.65) | < 0.001 | 15.88 (4.14-60.90) | < 0.001 |

Data are present as a ratio (94% CI).

CI, confidence interval; COPD, chronic obstructive pulmonary disease; BAL, bronchoalveolar lavage; TBLB, transbronchial lung biopsy.