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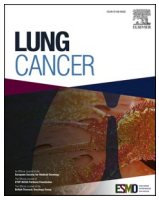

Research Paper

Midazolam with fentanyl for endobronchial ultrasound-guided transbronchial needle aspiration: a randomized, double-blind, phase III study

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ABSTRACT

Background: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a common technique for sampling mediastinal and hilar lymph nodes. However, the optimal sedation for EBUS-TBNA remains unclear. We aimed to evaluate the efficacy of adding fentanyl to midazolam.

Materials and methods: We conducted a single-center, randomized, double-blind, phase III study. Patients who received midazolam with fentanyl (fentanyl group) were compared with those who received midazolam with placebo (placebo group) during EBUS-TBNA. The primary outcome was the proportion of patients meeting all three criteria: 1) adequate sedation (Modified Observer's Assessment of Alertness and Sedation scale $\leq$4 or bispectral index values $\leq$80), 2) minimal additional sedation requirement (no more than two additional sedative administrations within the first 30 min), and 3) successful procedure completion (at least three EBUS-TBNA punctures).

Results: A total of 84 patients (fentanyl group, 41; placebo group, 43) were enrolled. There were no significant differences in patient characteristics between the two groups. The primary outcome was significantly better in the fentanyl group than in the placebo group (46.3 % vs. 23.3 %, p = 0.038). A significantly lower rate of sedative-induced delirium, a lower number of additional sedative administrations, and a higher rate of $\geq$3 punctures were observed in the fentanyl group. There were no significant differences in complications. The operator visual analog scale questionnaire on cough, sputum, cooperation, and sedative effects was significantly better in the fentanyl group.

Conclusion: Adding fentanyl to midazolam provided better sedation. Midazolam combined with fentanyl should be considered during EBUS-TBNA.

1. Introduction

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is commonly used not only for cytological material, but also for histological sampling of mediastinal or hilar lymph nodes or masses, and for next-generation sequencing [1–3]. To ensure safe and reliable biopsies, it is important to improve the tolerability of the procedure.

The British Thoracic Society (BTS) guidelines for diagnostic flexible bronchoscopy (FB) recommend intravenous sedation using midazolam, propofol, or opioids for patients without contraindications [4,5]. However, no standardized protocol exists regarding the type, dosage, or administration of sedatives during FB [6–10].

Coughs during FB are reportedly associated with patient discomfort [11]. Considering that EBUS-TBNA is a predictive factor for severe cough during FB [11], effective cough suppression is essential. Midazolam, which has the shortest half-life among traditional benzodiazepines, is commonly used for FB sedation [6,9]. Fentanyl, which has a

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rapid onset of action and a short plasma half-life due to its lipophilic nature, suppresses cough during FB by suppressing cough centers such as μ-receptor and possibly κ-receptor [12,13]. While propofol is also utilized for EBUS-TBNA, its narrow therapeutic window necessitates administration by trained physicians or anesthesiologists for conscious sedation [4,8]. Midazolam and fentanyl are considered standard and commonly used for FB sedation. However, the BTS and American College of Chest Physicians guidelines refer to only 2 randomized and double-blind reports on adding opioids to benzodiazepines, such as midazolam vs. alfentanil vs. midazolam with alfentanil and midazolam vs. midazolam with hydrocodone, as the basis for combining opioids and benzodiazepines [4,8,12,14], and there are no randomized, double-blind studies comparing their efficacy of midazolam with fentanyl compared to midazolam alone. The evidence for midazolam with fentanyl is not well established, and the optimal sedation for EBUS-TBNA remains unclear.

While the depth of sedation during FB is traditionally evaluated using the Ramsay Sedation Score [15], Richmond Agitation-Sedation Scale [16], and Modified Observer's Assessment of Alertness and Sedation (MOAA/S) scale [17], these methods rely on subjective assessments and may interfere with sedation. To overcome these limitations, we employed the bispectral index (BIS) monitor as an objective assessment tool [18].

To determine the optimal sedation for EBUS-TBNA, we conducted a randomized, double-blind, and phase III study comparing midazolam plus fentanyl versus midazolam alone.

2. Materials and methods

2.1. Study design

This single-center, prospective, randomized, double-blind, phase III study was approved by the Institutional Ethics Committee of Kobe University Hospital (C210004) on November 5, 2021, and was registered in the Japan Registry of Clinical Trials (jRCTs051210131). The study adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained from all the patients.

2.2. Patients

We enrolled patients aged 20 or older who required EBUS-TBNA for mediastinal or hilar lymph nodes or masses at Kobe University Hospital between December 2021 and October 2023. Patients with allergies to midazolam or fentanyl, or those using strong opioids such as morphine, methadone, fentanyl, oxycodone, buprenorphine, tapentadol, hydromorphone, and oxymorphone, were excluded.

Using electronic data capture software (Research Electronic Data Capture), patients were randomized 1:1 to receive either fentanyl or placebo through a stratified substitution block method. Stratification was based on the convex-probe EBUS scope model (BF-UC260FW or BF-UC290F; Olympus, Tokyo, Japan). To maintain double-blinding, all procedure participants (patients, operators, physicians, and nurses) remained unaware of group assignments throughout the procedure. While a physician prescribed both fentanyl and 0.9 % saline, unblinded pharmacists, working outside the bronchoscopy room, prepared either the study drug [fentanyl (2 mL, 100 μg) diluted with 8 mL of 0.9 % saline] or placebo (10 mL of 0.9 % saline). The prepared solution was provided to the physician labeled only as "study drug" and returned to the pharmacist post-procedure.

2.3. Procedure

Oxygen saturation (SpO_2), heart rate (HR), respiratory rate and BIS were monitored continuously and recorded every 2.5 min. Blood pressure (BP) was measured and recorded every 2.5 min during the procedure. The MOAA/S scale [17,19] (Supplemental Table 1) was assessed and recorded by a physician responsible for sedation at least every five minutes. All patients received supplemental oxygen starting at 2 L/min, increased up to 15 L/min via nasal cannula or face mask to maintain SpO_2 ≥90 %. A high-flow nasal cannula was used in cases where severe hypoxemia was a concern during the examination.

Before the procedure, patients received 6 mL of 2 % viscous lidocaine orally and 5 mL of 4 % lidocaine was sprayed into the pharynx. The sedating physician administered 2 mg of midazolam and 3 mL of fentanyl (30 μg)/placebo intravenously three minutes before FB insertion. For patients 75 or older or weighing less than 45 kg, the dose was reduced to 1 mg of midazolam and 2 mL of fentanyl (20 μg)/placebo. Experienced respiratory physicians performed the procedures. The operator inserted the FB (BF-P290, 1T260, 1TQ290, Q290, and H1200; Olympus, Tokyo, Japan), administered 2 % lidocaine to the vocal cord and airway epithelium, observed the airway, and replaced the FB with a convex-probe EBUS scope. After observing the lymph nodes using EBUS, TBNA was performed with a 22-gauge needle (NA-201SX-4022 or NA-U401SX-4022; Olympus, Tokyo, Japan). If patients appeared intolerable or had MOAA/S scale ≥5, BIS value ≥90, systolic BP ≥200 mmHg, diastolic BP ≥120 mmHg, or HR ≥130 bpm, they received additional 1 mg of midazolam and 1 mL of fentanyl (10 μg)/placebo simultaneously up to four times, at least four minutes apart, as required. Nicardipine (0.2 mg) was administered intravenously for uncontrolled hypertension if needed. The procedure was interrupted as needed if systolic BP was ≥200 mmHg, ≤80 mmHg, diastolic BP was ≥120 mmHg, ≤40 mmHg, or HR was ≥130 bpm, or ≤40 bpm. If BP was <180/110 mmHg and HR was ≤130 bpm or ≥40 bpm, the procedure was restarted. The number of interruptions and their duration that met the interruption criteria were recorded. In case of over-sedation, defined as a sustained MOAA/S scale 0 or 1, 0.25 mg of flumazenil was administered intravenously regardless of whether the patient was in the fentanyl or placebo group, and group assignment was revealed by the pharmacist while maintaining patient blinding. And then, if the patient was in the fentanyl group, 20 μg of naloxone was administered repeatedly every two minutes until arousal. Rapid On-Site cytologic Evaluation was performed when considered necessary by the operator. The operator completed the procedure based on an overall assessment of the amount of specimen collected and the burden on the patient. The procedure duration was defined from initial sedation administration to convex-probe EBUS scope removal. After the procedure, the operator answered six questions on a 100 mm visual analog scale (VAS), with higher scores indicating worse outcomes (Supplemental Fig. 1). If the assigned group was unblinded due to oversedation, the operator did not answer the questionnaire. One hour after the procedure, patients answered nine questions on a 100 mm VAS with higher scores indicating worse outcomes (Supplemental Fig. 2). We also assessed the patients' symptoms after the procedure.

2.4. Outcomes

The primary outcome was defined as the proportion of patients meeting all three criteria: 1) adequate sedation (MOAA/S scale ≤4 or BIS value ≤80), 2) minimal additional sedation requirement (no more than two additional administrations of midazolam and fentanyl/placebo within 30 min of the first administration, and 3) successful procedure completion (three or more EBUS-TBNA punctures). We also assessed the efficacy outcomes (VAS questionnaire of the patient and operator, dose of midazolam, fentanyl, and lidocaine, and diagnostic accuracy which was the ratio of patients with a confirmed diagnosis by EBUS-TBNA to those with a final diagnosis by EBUS-TBNA or other tests) and safety outcomes (MOAA/S scale, BIS value, vital signs during the procedure, duration of the procedure, and number and duration of interruptions).

2.5. Sample size

We conducted a retrospective review of patients who underwent FB and were scheduled for EBUS-TBNA at our hospital between May 2020

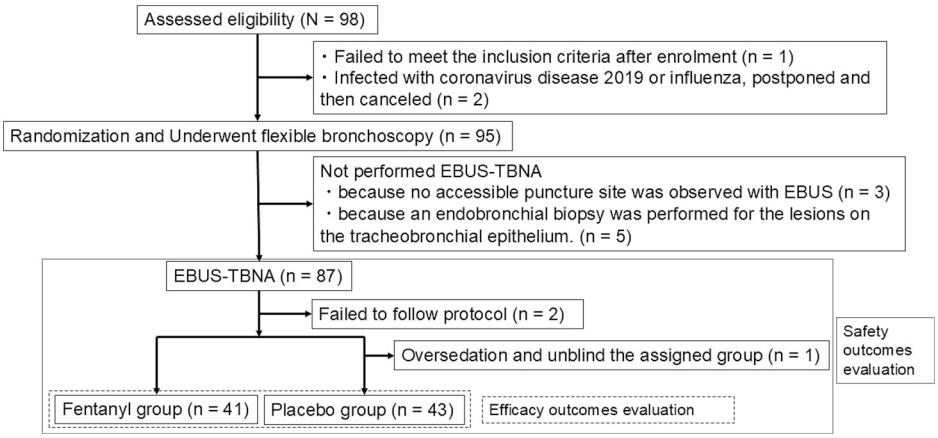

Fig. 1. Consort diagram. EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration.

and July 2021. The primary endpoint was met by 25 % of patients who received midazolam alone and 42.9 % of those who received midazolam with fentanyl or meperidine. In this hospital, opioids are not used routinely for FB, but when deemed necessary by the operator. To account for this potential selection bias in the midazolam with fentanyl or meperidine group, we assumed a larger difference (25 % for midazolam with placebo vs. 55 % for midazolam with fentanyl) in our study if patient characteristics are homogeneous in the placebo and fentanyl groups. A two-sided type I error rate of 0.05 and a target power of 80 % led to sample sizes of 41 patients in each group.

2.6. Statistical analysis

Statistical analyses were performed using EZR software, version 1.51 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [20]. Quantitative variables are presented as mean and standard deviation or median and range, as appropriate. Categorical variables are presented as percentages. Fisher's exact test was used to compare the rate of meeting the primary endpoint between groups and categorical variables. A *t*-test or Mann-Whitney *U* test was used to compare quantitative variables. Statistical significance was set at p value < 0.05.

3. Results

3.1. Patient characteristics

Of the 98 patients enrolled, one did not meet the inclusion criteria, and two were infected with coronavirus disease-2019 or influenza and subsequently canceled. Of the 95 patients randomized and undergoing FB, EBUS-TBNA was not performed in eight due to the lack of an accessible puncture site or the preference for an endobronchial biopsy over EBUS-TBNA. Excluding these patients, 87 were evaluated for safety outcomes (fentanyl group, n = 43; placebo group, n = 44). Excluding two patients who deviated from the protocol and one who was oversedated and unblinded, 84 patients were evaluated for efficacy outcomes (fentanyl group, n = 41; placebo group, n = 43) (Fig. 1). One unblinded patient was assigned to the placebo group and received 1 mg of midazolam. Of the two patients who deviated from the protocol, one was received incorrectly 3 mg of midazolam as the first administration, and the other did not received midazolam and fentanyl/placebo simultaneously incorrectly. There were no significant differences in characteristics between the fentanyl and placebo groups (Table 1). The final diagnoses were primary lung cancer in 55 patients (63.2 %), sarcoidosis in seven patients (8.0 %), metastatic lung cancer in six patients (6.9 %), malignant mesothelioma in one patient (1.1 %), and non-diagnosis in 18 patients (20.7 %). Rapid On-Site cytologic Evaluation was performed in 3 (3.4 %) patients, with one negative patient having an additional puncture from a different site, ultimately remaining non-diagnostic.

3.2. Outcome

The primary outcome (the proportion of the patients meeting all of the following criteria: 1) MOAA/S scale $\leq$4 or BIS value $\leq$80, 2) no more than two additional administrations of midazolam and fentanyl/placebo within 30 min of the first administration, and 3) three or more punctures) was significantly better in the fentanyl group compared to the placebo group (46.3 % vs. 23.3 %; p = 0.0384) (Table 2). There were 9 operators and 8 physicians responsible for sedation, and no significant difference in the proportion of achievement of the primary outcome was shown between the individual operators (p = 0.865) or between the individual physicians responsible for sedation (p = 0.216).

In evaluating efficacy outcomes, the fentanyl group required

Table 1
Patient characteristics.

Characteristics	All (N = 87)	Fentanyl group(n = 43)	Placebo group (n = 44)	p value
Age, median (median, range)	77 (37–86)	72 (37–84)	72 (39–86)	0.956
Male (%)	55 (63.2)	28 (65.1)	27 (61.4)	0.825
Body weight (kg, mean, SD)	58.0 ± 10.8	58.4 ± 10.3	57.6 ± 11.3	0.729
Elevation of AST or ALT (%)	16 (18.4)	9 (20.9)	7 (15.9)	0.59
Elevation of Cre (%)	17 (19.5)	9 (20.9)	8 (18.2)	0.792
SBP before the procedure (mmHg, mean, SD)	143 ± 22.0	141 ± 17.9	144 ± 25.6	0.54
DBP before the procedure (mmHg, mean, SD)	81 ± 11.0	82 ± 8.5	81 ± 13.1	0.652
HR before the procedure (beats/minute, mean, SD)	76 ± 13.2	76 ± 13.1	76 ± 13.4	0.981
Convex probe EBUS scope, BF-UC260FW (%)	36 (41.4)	18 (41.9)	18 (40.9)	1
Duration of the procedure (minute, median, range)	35.7 (12.9–51.5)	37.4 (18.3–51.5)	35.6 (12.9–50.2)	0.567

SD, standard deviation; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Cre, creatinine; sBP, systolic blood pressure; dBP, diastolic blood pressure; HR, heart rate; EBUS, endobronchial ultrasound.

Table 2
Primary outcome.

	All (N = 84)	Fentanyl group (n = 41)	Placebo group (n = 43)	p value
Primary outcome [all of the following; 1), 2), and 3)], (%)	29 (34.5)	19 (46.3)	10 (23.3)	0.038
1) MOAA/S scale ≤4 or BIS value ≤80 (%)	81 (96.4)	39 (95.1)	42 (97.7)	0.611
2) No more than two additional midazolam and fentanyl/placebo administrations within the first 30 min (%)	38 (45.2)	23 (56.1)	15 (34.9)	0.079
3) Three or more EBUS-TBNA punctures (%)	64 (76.2)	36 (87.8)	28 (65.1)	0.021

MOAA/S, Modified Observer's Assessment of Alertness/Sedation; BIS value, bispectral index value; EBUS-TBNA, Endobronchial ultrasound-guided transbronchial needle aspiration.

Table 3
Sedation and analgesia.

	All (N = 84)	Fentanyl group (n = 41)	Placebo group (n = 43)	p value
Dose of the first administration of midazolam (mL, median, range)	2 (1–2)	2 (1–2)	2 (1–2)	0.535
Total dose of midazolam (mL, median, range)	5 (2–6)	4 (2–6)	5 (3–6)	0.056
Dose of the first administration of fentanyl/placebo (mL, median, range)	3 (2–3)	3 (2–3)	3 (2–3)	0.535
Total dose of fentanyl/placebo (mL, median, range)	6 (3–7)	5 (3–7)	6 (4–7)	0.056
Total number of administrations of midazolam and fentanyl/placebo (median, range)	4 (2–5)	4 (2–5)	4 (2–5)	0.04
Number of additional midazolam and fentanyl/placebo administrations within 30 min (median, range)	3 (1–4)	2 (1–4)	3 (1–4)	0.04
Total dose of lidocaine (mL, mean, SD)	13.9 ± 2.3	13.6 ± 2.2	14.3 ± 2.3	0.183

Midazolam (2 mL, 10 mg) was diluted with 8 mL of 0.9 % saline, fentanyl (2 mL, 100 μg) was diluted with 8 mL of 0.9 % saline, and placebo was 10 mL of 0.9 % saline. SD, standard deviation.

significantly fewer total and additional sedative administrations compared to the placebo group (Table 3). Additionally, the fentanyl group achieved a higher rate of completing ≥3 punctures. Eight patients did not achieve MOAA/S scale ≤4, but five of these achieved BIS value ≤80. Conversely, 15 patients did not achieve a BIS value ≤80, but 12 of these achieved a MOAA/S scale ≤4. Among the 67 patients with a final diagnosis by EBUS-TBNA, surgery, or computed tomography-guided biopsy, the diagnostic accuracy was 92.5 % (62 patients). There was no significant difference in diagnostic accuracy between the fentanyl and placebo groups [32 patients (94.1 %) vs.30 patients (90.9 %); p = 0.673]. Patients with three or more punctures had significantly better diagnostic accuracy than those with two or fewer punctures (98 % vs. 76.5 %; p = 0.013), and no significant difference was shown in the diagnostic accuracy between three and four or more puncture (100 % vs. 95 %; p = 0.4).

A comparison of the VAS questionnaire of the patient and operator between the fentanyl and placebo groups is shown in Fig. 2. There was no significant difference in the patient VAS questionnaire scores between the two groups. However, the operator VAS questionnaire scores on patient cough, sputum, effective sedation, and patient cooperation were significantly better in the fentanyl group. There were also trends toward better operator VAS questionnaire scores for patient dyspnea (p = 0.0977) and satisfaction (p = 0.0577) in the fentanyl group.

The safety outcomes are presented in Table 4. The fentanyl group demonstrated a lower incidence of sedative-induced delirium (MOAA/S scale 6). There were no significant differences in the rates of unexpected deep sedation (MOAA/S scale ≤1), hypopnea (respiratory rate ≤10 breaths/minute), lowest SpO_2, and circulatory dynamics between the fentanyl and placebo groups. The rate of patients who received nicardipine was significantly higher in the placebo group, [0 patients vs.8 patients (18.2 %); p < 0.01]. There was no significant difference in the highest oxygen flow rate between the two groups during the procedure, and all patients were weaned off supplemental oxygen on the procedure day. There were no significant differences between the two groups in the rates of the patients meeting the interruption criteria, or in the number and the duration of interruptions. Nineteen patients (21.8 %) met the interruption criteria for systolic BP ≥ 200 mmHg, 19 (21.8 %) for diastolic BP ≥ 120 mmHg, 7 (8 %) for HR ≥ 130 beats/minute, and 1 (1.1 %) for hypotension (systolic BP ≤ 80 mmHg, diastolic BP ≤ 40 mmHg). Of the two patients who received flumazenil for oversedation, one was unblinded and found to be in the placebo group. The other was not unblinded, because the patient awoke before the unblinded pharmacist revealed the group assignment. One patient in the placebo group developed postoperative mediastinitis.

4. Discussion

To the best of our knowledge, this is the first phase III study to evaluate the efficacy and safety of midazolam in combination with fentanyl in patients undergoing EBUS-TBNA. Our assessment of sedation efficacy incorporated three key components: sedation depth, frequency of additional sedative administration, and adequacy of tissue sampling.

The BTS guidelines describe the desired depth of sedation as one that allows verbal commands to the patient during the procedure, equivalent to the MOAA/S: 3–4 [4]. Previously, we showed that the median BIS values for MOAA/S scale 3–4 were 82.0 during FB [21]. Therefore, we defined the appropriate depth of the sedation as MOAA/S scale ≤4 or BIS value ≤80. In the present study, most patients in both groups achieved this target sedation depth. While both groups achieved target sedation depths, the fentanyl group required lower midazolam doses, suggesting that fentanyl co-administration enables reduced benzodiazepine requirements while maintaining adequate sedation.

We defined effective sedation maintenance as the number of no more than two additional sedative drug administrations within 30 min of the first administration. The fentanyl group demonstrated significantly fewer additional sedative requirements, indicating better sedation stability. Similarly, the addition of pethidine to midazolam for FB sedation resulted in significantly fewer additional sedatives in the combined group [22,23]. Concomitant sedation may reduce the frequency of patient arousal during FB and maintain sedation depth.

Regarding the number of punctures, Lee *et al.* reported a diagnostic accuracy rate of 89.7 % for a single puncture, 94.4 % for two punctures, and 98.4 % for three or four punctures in EBUS-TBNA for cancer [24]. We thus defined three or more punctures as adequate for sample collection. The rate of at least three punctures was significantly higher in the fentanyl group, suggesting that better sedation may lead to adequate specimen collection.

In this study, the fentanyl group scored better on the operator questionnaire, while there were no significant differences in the patient questionnaire. Cömert *et al.* reported that both patient and operator satisfaction were significantly better in the midazolam and fentanyl groups than in the midazolam-alone group in EBUS-TBNA [25].

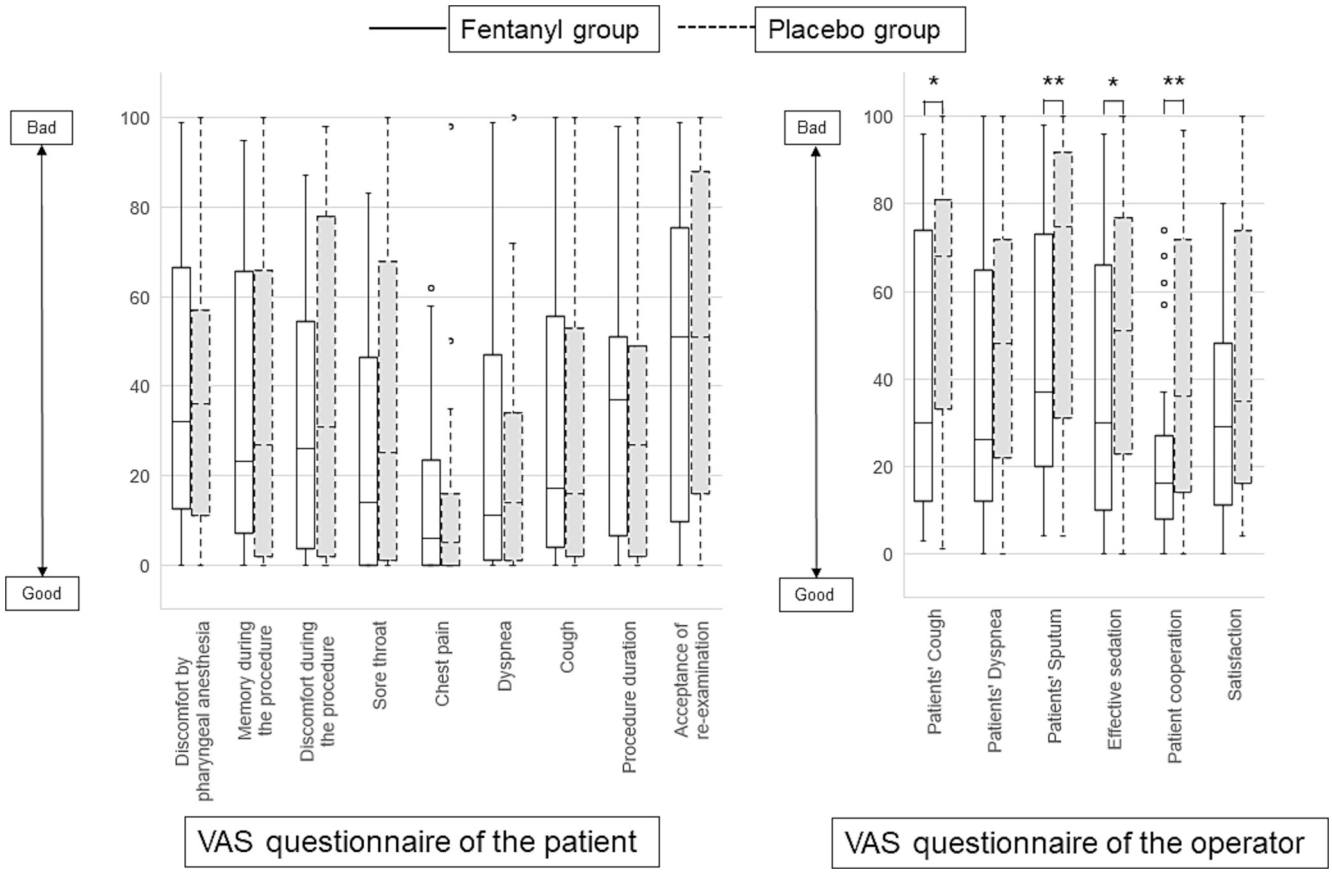

Fig. 2. VAS questionnaire scores of the patient and operator. Higher scores indicated worse outcomes. VAS, visual analog scale; *, $p < 0.05$; **, $p < 0.01$.

Although the open-label, nonrandomized nature of this study may have prevented an accurate assessment, the difference between the two groups was more pronounced in the operator questionnaire than in the patient questionnaire. This discrepancy may reflect anterograde amnesia from sedation [26], particularly since our patient questionnaires were administered 60 min post-procedure. Previous research has shown that midazolam doses comparable to those used in our study can induce amnesia in 20–50 % of patients at 60 min post-administration [27]. Thus, the operator might be more accurate than the patient in assessing the effectiveness of sedatives.

The addition of fentanyl did not increase the incidence of sedation-related complications. A previous study comparing midazolam alone with midazolam plus fentanyl as a sedative during FB found no differences in complications between the two groups [28]. Acceptable complication rates were also reported in another study that used midazolam plus fentanyl for FB sedation [29]. In our study, the proportion of patients with sedative-induced delirium was significantly lower in the fentanyl group. Previous reports have indicated that high-dose benzodiazepines are slightly more associated with delirium than low-dose benzodiazepines [30], and the addition of pethidine to midazolam for FB sedation resulted in significantly fewer cases of sedative-induced delirium in the combined group [23]. In our study, the fentanyl group tended to receive less midazolam than the placebo group, suggesting that a reduced midazolam dose in combination with fentanyl contributed to a lower incidence of sedative-induced delirium. A combination of midazolam and fentanyl can be safely used as a sedative during EBUS-TBNA.

General anesthesia (GA) is another commonly used sedation technique for EBUS-TBNA [31]. Casal *et al.* reported that conscious sedation with midazolam and fentanyl was comparable to GA in terms of the number of biopsies, diagnostic accuracy, complication rate, and tolerance during EBUS-TBNA [32]. However, not all facilities have access to anesthesiologists or operating rooms during FB. Agostini *et al.* reported that EBUS-TBNA under conscious sedation without an anesthesiologist was associated with a 27 % reduction in cost compared to GA [33]. Conscious sedation with midazolam and fentanyl is preferred for EBUS-TBNA.

In this study, some patients did not achieve a MOAA/S scale $\leq$4 but achieved a BIS value of $\leq$80, while others did not achieve a BIS value of $\leq$80 but achieved a MOAA/S scale $\leq$4. BIS values and scales, such as the MOAA/S scale, may be better used in combination, if necessary, to assess the appropriate depth of sedation and reduce unnecessary additional sedative administration.

5. Conclusion

We demonstrated the efficacy and safety of midazolam combined with fentanyl in patients who underwent EBUS-TBNA. Based on these

Table 4
Safety outcomes evaluation.

	All (N = 87)	Fentanyl group (n = 43)	Placebo group (n = 44)	p value
Unexpected deep sedation (MOAA/S scale 0 or 1) (%)	13 (14.9)	7 (16.3)	6 (13.6)	0.772
Sedative-induced delirium (MOAA/S scale 6) (%)	24 (27.6)	7 (16.3)	17 (38.6)	0.03
Lowest BIS value (median, range)	75 (39–86)	74 (59–86)	76 (39–84)	0.866
Highest BIS value (median, range)	98 (82–98)	98 (85–98)	98 (82–98)	0.611
Flumazenil (%)	2 (2.3)	1 (2.3)	1 (2.3)	1
Naloxone (%)	0	0		
Lowest SpO_2 (%, median, range)	91 (67–99)	90 (67–99)	91.5 (75–96)	0.187
Highest oxygen flow (L/min, median, range)	4 (2–40)	4 (2–15)	4 (2–40)	0.917
Hypopnea (respiratory rate ≤10 breaths/minute) (%)	21 (24.1)	13 (30.2)	8 (18.2)	0.218
Tachypnea (respiratory rate ≥20 breaths/minute) (%)	85 (97.7)	41 (95.3)	44 (100)	0.241
Rate of meeting the interruption criteria (%)	31 (35.6)	13 (30.2)	18 (40.9)	0.372
Number of interruptions (median, range)	0 (0–3)	0 (0–3)	0 (0–3)	0.314
Duration of interruption (minute)	0 (0–20.9)	0 (0–20.9)	0 (0–12)	0.339
Bradycardia (heart rate ≤40 beats/minute) (%)	0	0	0	
Tachycardia (heart rate ≥130 beats/minute) (%)	6 (6.9)	2 (4.7)	4 (9.1)	0.676
Hypotension (sBP ≤80 mmHg or dBP ≤40 mmHg) (%)	1 (1.1)	0	1 (2.3)	1
Hypertension (sBP ≥ 200 mmHg or dBP ≥ 120 mmHg) (%)	26 (29.9)	9 (20.9)	17 (38.6)	0.101

MOAA/S, Modified Observer's Assessment of Alertness/Sedation; BIS value, bispectral index value; SpO_2, percutaneous oxygen; sBP, systolic blood pressure; dBP, diastolic blood pressure.

findings, midazolam with fentanyl should be considered for conscious sedation during EBUS-TBNA.

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CRediT authorship contribution statement

Jun Yamada: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Daisuke Hazama:** Writing – review & editing, Methodology, Investigation. **Takafumi Fukui:** Writing – review & editing, Investigation. **Atsuhiko Yatani:** Writing – review & editing, Investigation. **Mariko Okamoto:** Writing – review & editing, Investigation. **Shodai Fujimoto:** Writing – review & editing, Investigation. **Ryosuke Yoshimura:** Writing – review & editing, Investigation. **Mizuki Takayasu:** Writing – review & editing, Investigation. **Naoya Takata:** Writing – review & editing, Investigation. **Hiroki Sato:** Writing – review & editing, Investigation. **Chihiro Mimura:** Writing – review & editing, Investigation. **Koichi Furukawa:** Writing – review & editing, Investigation. **Naoko Katsurada:** Writing – review & editing, Investigation. **Masatsugu Yamamoto:** Writing – review & editing, Investigation. **Motoko Tachihara:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: MT, NK, and MY received honoraria from OLYMPUS. The other authors declare no conflicts of interest.

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Appendix A. Supplementary data

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