A comparison of propofol–midazolam and midazolam alone for sedation in endobronchial ultrasound-guided transbronchial needle aspiration: a retrospective cohort study

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Abstract

Objectives: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a new, minimally invasive, bronchoscopic technique used in the evaluation of inthrathoracic lymph nodes.Use of sedation drugs before the procedure differs among centres. There is no standardization about sedation before EBUS-TBNA.We used a policy decision to shift from use of propofol with midazolam vs midazolam alone in a large tertiary hospital to evaluate the diagnostic yield and safety of EBUS-TBNA procedure.

Methods: Files of all the patients who were performed EBUS-TBNA between the dates of September 2010 and May 2014 were surveyed. All the EBUS-TBNA cases were performed under sedation of propofol and midazolam with an accompanying anesthesiologist in the beginning, however, sedation is applied with midazolam without an accompanying anesthesiologist after April 2013 due to changes in sedation policy. The diagnostic yield and complication rates were compared by chi-squared analysis between two groups.

Results: The files of 340 EBUS-TBNA performed patients were evaluated. Of the patients 274 eligible patients were analysed. 152 patients who fulfilled the inclusion criteria were analysed in propofol-midazolam (P) sedated group and 122 patients were analysed in midazolam (M) group. There is no statistically significant difference between two different sedated groups in terms of age and gender. Diagnostic value was detected as 77.6% in P group and 85.7% in M group and the difference was not statistically significant. No difference between complication rates of both groups was observed.

Conclusion: Both sedation-types for performing EBUS-TBNA showed similar diagnostic value and complication rates in our study. Propofol with midazolam application requires with an accompanying anaesthesiologist, therefore, it increases cost. EBUS-TBNA procedures had been performed in safe with no decrease in diagnostic yield under moderate sedation.

Please cite this paper as: Öztaş S, Aka Aktürk Ü, Alpay LA, Meydan B, Ogün H, Taylan M, Yalçınsoy M, Çalışır HC, Metin Görgüner A and Ernam D. A comparison of propofol–midazolam and midazolam alone for sedation in endobronchial ultrasound-guided transbronchial needle aspiration: a retrospective cohort study. *Clin Respir J* 2017; 11: 935–941. DOI:10.1111/crj.12442.

Key words
EBUS-TBNA – sedation – propofol – midazolam

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Received: 10 July 2015
Revision requested: 22 November 2015
Accepted: 14 December 2015

DOI:10.1111/crj.12442

Authorship and contributorship
Dr. Selahattin Öztaş contributed to the study design, data collection, EBUS performance, data interpretation and manuscript composition. He had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.He is one of the quarantor of the study. Dr. Ülkü Aka Aktürk contributed to the study design, Institutional Review Board application, EBUS performance, data collection, data interpretation, statistical analysis, manuscript composition and revision. She had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.She is the quarantor of the entire manuscript. Dr. Levent Alpay contributed to statistical analysis, data interpretation and manuscript composition and revision. Dr. Burhan Meydan contributed to Institutional Review Board application, patient

recruitment and data collection. Dr. Hamza Ogün, Dr. Murat Yalçınsoy contributed to Institutional Review Board application, data collection and data interpretation. Dr. Mahşuk Taylan contributed to the statistical analysis, data interpretation and manuscript composition and revision. Dr. Haluk Çalışır contributed to EBUS performance, data collection and interpretation Dr. Ali Metin Görgüner and Dr. Dilek Ernam contributed to study design, manuscript composition and revision.

Ethics

The study was approved by the local Ethics Committee of the Institution and was conducted in accordance with the ethical principles stated in the Declaration of Helsinki.

Conflict of interest

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

The abstract of this study was presented as a discussion poster in ERS Congress 2014 in Munich.

Introduction

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a new, minimally invasive, bronchoscopic technique used in the evaluation of inthrathoracic lymph nodes, mediastinal lesions and regional nodal staging of lung cancer. Diagnostic accuracy of EBUS-TBNA is high and it is an alternative method to mediastinoscopy (1). Although, EBUS-TBNA was typically performed using general anesthesia when first introduced about 10 years ago, it is now routinely performed by pulmonologists in an outpatient setting (1, 2).

Benzodiazepine and opiates are the most commonly used sedative agents for EBUS-TBNA.

Benzodiazepines are the most common used sedative agents due to their ease of application and speed of action. However, they may produce prolonged sedation and cognitive impairment (3–6). Midazolam is used to provide conscious sedation which has anxiolytic, amnestic and hypnotic effects. Propofol, a short-acting hypnotic agent, has been increasingly used to provide deep sedation in the endoscopy unit with an acceptable safety profile. It supress the cough better than the other agents and provides more comfortable procedure for bronchoscopist. Because it has a narrow therapeutic window beyond which general anaesthesia is achieved, propofol is advised to apply by a physician formally trained about propofol or by an anaesthetists (7).

EBUS-TBNA is usually performed under moderate sedation using narcotics and short acting benzodiazepines and local anesthesia. Because of its being more difficult than routine bronchoscopy due to the size of the scope and longer procedure time, it also can be performed under general anesthesia. However, the diagnostic advantages of general anesthesia for EBUS-TBNA have not been proved. Patient satisfaction by EBUS-TBNA under conscious sedation was reported to be high (1).

Currently there is no proof that any level of anesthesia deeper than the moderate sedation is required for performing the procedure. The main advantages of EBUS-TBNA are to be minimally invasive, ease as compared with surgical procedure as well as the economic advantage. Deeper level of sedation may decrease these advantages by including additional personnel and requiring operating room.

We used a policy decision to shift from use of propofol with midazolam vs midazolam alone in a large tertiary hospital to evaluate the diagnostic yield and safety of EBUS-TBNA procedure.

Materials and methods

Research setting

It is a retrospective cohort study. The files of EBUS-TBNA performed patients between the dates of September 2010–May 2014 were analysed. Patients who meet inclusion criteria were enrolled into the study. In our clinic, all EBUS-TBNA procedures were performed under propofol with midazolam sedation accompanied by anesthesiologists between the dates of September 2010 and Marc 2013. After April 2013, because of policy change, EBUS have been performed under midazolam sedation.

The study was approved by the local Ethics Committee of the Institution and was conducted in accordance with the ethical principles stated in the Declaration of Helsinki. Because the study was conducted retrospectively, patient approval form was not required. Institutional Review Board committee name was İstanbul Kartal Dr Lütfi Kırdar Kartal Education and Research Hospital Scientific Research and Assessment Committee, approval number was 89513307/1009/285.

Study participants

Files of all the patients who were performed EBUS-TBNA procedure in our hospital between the dates of September 2010 and May 2014 were surveyed. Files with missing information were excluded from the study. All the EBUS-TBNA cases were performed under sedation of propofol and midazolam with an accompanying anesthesiologist in the beginning however sedation is applied with midazolam without an accompanying anesthesiologist after April 2013 due to changes in sedation policy. EBUS-TBNA procedures were performed under propofol and midazolam sedation with an accompanying anesthesiologist due to patient demand in 13 cases in the period that midazolam sedation was performed without an accompanying anesthesiologist. These patients were excluded from the midazolam group. Included patients are shown on the flow chart (Fig. 1). The files of patients were analysed, age, gender, aspirated lymph nodes, sedation agents, diagnosis and complications were recorded. When EBUS-TBNA was non-diagnostic, other invasive surgical interventions were performed to reach final diagnosis.

EBUS-TBNA protocol

All the EBUS-TBNA procedures were performed by two experienced bronchoscopists. Oxygen saturation, blood pressure and pulses of patients were monitorized before and during the procedure. For local anesthesia, 10% xylocaine was applied to oropharynx and 2% aritmal was applied to all the patients. All the patients were given 2 L/min oxygen with nasal mask. In propofol–midazolam sedated group, anesthesiologist applied 0.05 mg/kg intravenous midazolam and 1 mg/kg propofol, then increased the doses according to Ramsey Sedation Scale (8). In midazolam sedated group, bronchoscopist applied 0.05 mg/kg midazolam and titrate the doses according to Ramsey Sedation Scale. Following sedation, the patients were intubated orally with an EBUS-guided TBNA bronchoscope (7.5 MHz, BF-UC160F; Olympus Optical Co. Tokyo, Japan). Mediastinal and hilar LNs were examined systematically by using Mountain's system (9) and measured. The lymph nodes over 0.5 cm were aspirated with dedicated 22 gauge needles (NA-201SX-4022-C; Olympus Tokyo, Japan). The aspirated material was smeared on glass slides and the remaining specimen was fixed in 90% alcohol for cytopathological evaluation. On-site examination was not performed. On cytopathological examination, the puncture was considered adequate when lymphocytes were seen in the smear.

Study outcomes

Our primary outcomes are diagnostic yield and complication rate. EBUS-TBNA results were considered malignant when the aspirated material contained malignant cells. A diagnosis of tuberculosis or sarcoidosis was made based on cytopathology that showed the presence of caseating or non-caseating granuloma, in addition to clinical, radiological and microbiological findings. Any diagnosis other than malignancy required further surgical investigation or radiologic follow-up for at least 6 months. On follow-up, LNs that persisted in size, diminished or resolved were considered benign.

Complications were recorded as major and minor. Unstoppable hemorrhages that required surgical intervention, arrhythmias that required cardioversion, pulmonary insufficiency that required admittance of the patient as inpatient were accepted as major complications. Self-restricting bleedings, desaturations that were balanced with oxygen support, hypotension that were recovered with fluid administration were accepted as minor complications. Saturation below 85% for longer than 1 min besides nasal 2 L/min oxygen administration was accepted as desaturation. Decrease of systolic blood pressure 20 mmHg or more from the basal reference of the patient was accepted as hypotension. All the patients were under observation for 4–6 h. Patients with modified Aldrete score of 9 or above were discharged.

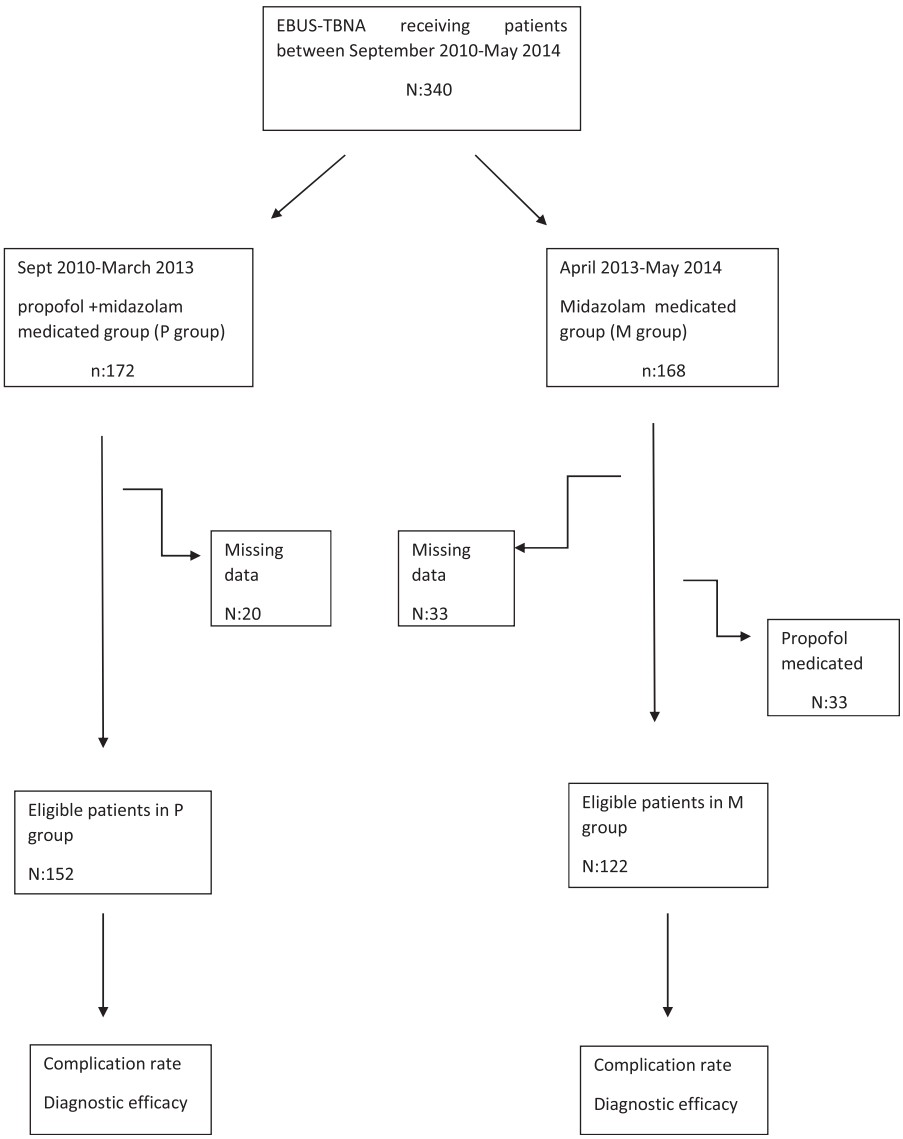

Figure 1. Flow chart.

Statistical method

Descriptive statistics (age, gender values) were as frequency, percentage, mean value and standard deviation (SD). For comparison of the cathegorical variables, chi-squared test was used. While parametric (*t*-test) test was used for normally distributed continous variables, non-parametric test (Mann–Whitney *U*-test) was used for variables with non-normal distibution. Logistic regression analysis was performed to compare the diagnostic yield between two different sedated group adjusted to age, gender and number of aspirated lymph nodes per patient. A P value of < 0.05 was considered significant for statistical evaluation. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) 17.0 (SPSS, Inc., Chicago, IL, USA).

Results

The files of 340 EBUS-TBNA performed patients were evaluated. Of the patients 274 eligible patients were analysed. One hundred and fifty two patients who fulfilled the inclusion criteria were analysed in propofol-midazolam sedated group and 122 patients were analysed in midazolam group. Median age of propofol (P) group was 56.8 ± 11.1 while the median age of midazolam (M) group was 56.1 ± 12.2 and the difference was not statistically significant ($P = 0.64$). Male patient ratio was 73.7% in M group and 70.9% in P group and the difference was not statistically significant ($P = 0.55$).

There is no statistically significant difference between propofol with midazolam sedated and midazolam

Table 1. Characteristics of two different sedated groups

	Propofol and Midazolam sedated group 9/2010–3/2012) *N*:152	Midazolam alone sedated group (4/2014–5/2013) *N*:122	*P* value
Age	56.8 ± 11.1	56.1 ± 12.2	0.64
Male gender	%73.7	%70.9	0.55
Number of aspirated lymph nodes per patient	1.33 ± 0.5	2.21 ± 1.3	0.001

alone sedated groups in terms of age and gender (Table 1).

The most common aspirated lymph node stations were seven (subcarinal) (%61.6), 4R (%52.1), 4L (%19.0), 10R (%14.9). The number of aspirated lymph nodes per patient was 2.21 ± 1.3 in midazolam sedated group, 1.33 ± 0.5 in propofol with midazolam sedated group. The difference is statistically significant ($P = 0.001$).

Diagnostic value was detected as 77.6% in P group and 85.7% in M group and the difference was not statistically significant ($P = 121$). No difference between complication rates of both groups was observed ($P = 0.14$; Table 2).

If we compare the diagnostic yield between two different groups adjusted to age and gender, the difference is not statistically significant ($P = 0.74$, $P = 0.38$; Table 3). Adjusted to number of aspirated lymph nodes per patients, it was higher in M group than P group ($P = 0.001$; Table 3).

Discussion

Sedation is recommended in bronchoscopy guidelines for comfort and harmony of both the doctor and the patient during conventional fiberoptic bronchoscopy (7). The need for sedation is more during EBUS-TBNA as it has a thicker structure then standard fiberoptic bronchoscopes and an angled optic and intense mucosal contact for obtainment of ultrasonic image. EBUS-TBNA was performed under general anesthesia previously, however, nowadays it is usually performed under moderate sedation with narcotic agents and short-acting benzodiazepines (1). No diagnostic advantage of the procedure was proven if it is performed under general anesthesia.

In our study, EBUS-TBNA procedures were performed under deeper sedation of propofol and midazolam with accompanying anesthesiologist in the beginning, however due to the changes in sedation policy in our hospital EBUS-TBNA procedures were begun to be performed under moderate sedation of midazolam after a certain date. Therefore, we have analysed if there was a difference between diagnostic value and complication rates of these two periods of time in relation to the sedation difference during EBUS-TBNA procedures. In conclusion, no statistically significant difference was observed between the diagnostic values of the two groups. No major complications were observed in both groups, minor complication rates were similar and there was no statistically significant difference observed.

The British Thoracic Society (BTS) advices two level B evidence comments within their guidelines (7, 10). The BTS recommends usage of sedation for all patients undergoing bronchoscopy unless contraindicated and usage of incremental doses of sedation during the procedure. The BTS defined the need for sedation as being based on patient comfort and satisfaction but also commented that usage of sedation will most likely allow for easier procedural performance. BTS guidelines recommend application of propofol by an anesthesiologist or specially trained physician. In many centres, propofol is applied by an anesthesiologist in bronchoscopy and endoscopy units.

Table 2. Diagnostic yield and complication rate of two different premedicated EBUS-TBNA performed groups

	P GROUP propofol with midazolam sedated group *n*:152	M GROUP Midazolam sedated group *n*:122	*P* value
Diagnostic yield/sensitivity	%77.6	%85.7	0.121
CI	95%(70%–83.8%)	%95(%77.9–%91.1)	
Complication rate	%6.9	%3.2	0.14
CI	95%(%3.6–%12.5)	%95(%1.0–%8.6)	

CI, confidence interval.

Table 3. Comparison of diagnostic yield between two different sedated group adjusted to age, gender and number of aspirated lymph nodes per patient

	OR	%95 CI	*P* value
Age	1.04	0.98–1.02	0.74
Gender	0.77	0.42–1.4	0.38
Number of aspirated lymph nodes/patient	0.27	0.2–0.42	0.001

OR, odds ratio; CI, confidence interval.

In 2011, the ACCP published recommendations for the performance of bronchoscopic procedures, including flexible bronchoscopy and EBUS. The ACCP suggested that all physicians performing bronchoscopy consider using topical anesthesia, analgesic and sedative agents when feasible for the performance of flexible bronchoscopy, but no specific guidelines regarding moderate vs deep sedation were addressed (4).

There are studies comparing anesthesia methods during conventional fibre-optic bronchoscopy and EBUS-TBNA in the literature. Studies comparing sedation methods with each other or general anesthesia according to depth, especially those evaluating patient and bronchoscopist satisfaction, procedural success, duration and safety stand out. However, there are only a few studies comparing the diagnostic value of the procedure in relation to the sedation methods performed during EBUS-TBNA.

Stolz *et al.* compared propofol and midazolam-hydrocodone combination during flexible bronchoscopy and evaluated the mean lowest arterial oxygen saturation and readiness for discharge score 1 h after procedure. It was observed that the mean lowest arterial oxygen saturations were similar in both groups, however, duration until discharge was shorter in propofol group. It was stated that propofol is as safe and efficient as combined sedation and might be preferred if timely discharge is the priority (11). In another study, conducted by Stolz *et al.* it was proven that combined sedation methods performed with benzodiazepines and opioids are safe and efficient (12).

Schlatter *et al.* compared propofol and propofol + hydrocodone during flexible bronchoscopy procedures. Procedure duration, time until discharge and complication rates were found to be similar in both groups, however, the mean cough score was lower in propofol + hydrocodone group and lower dosages of propofol had been required for the patients in this group (13).

Yarmus *et al.* reported that sampled lymph node numbers was more in deep sedation group and diagnostic value was higher in this group than moderate sedation group in their study comparing moderate and deep sedation during EBUS-TBNA procedures (14). Jeyabalan *et al.* stated that conscious sedation with fentanyl and midazolam during EBUS-TBNA was well-tolerated and the patients stated that they would undergo another procedure if necessary (15).

Postelnicu *et al.* compared procedure duration and hospital-stay between moderate and deep sedation during EBUS-TBNA procedure and found that procedure duration was shorter in deep sedation with continuous propofol infusion group than the moderate sedation with fentanyl and midazolam group; however, the difference was not statistically significant. Hospital-stay was significantly shorter in moderate sedation group (16). Casal *et al.* reported that EBUS-TBNA performed under moderate sedation (midazolam + fentanyl) results in comparable diagnostic yield, rate of major complications and patients' tolerance as general anesthesia in a randomized trial (17).

In our study, diagnostic efficacy of conscious sedation with midazolam was found similar to sedation with propofol group during EBUS-TBNA. One of the most important restrictions of our study is that no information about patient and bronchoscopist satisfaction is obtained due to the retrospective structure of the study. In addition, procedures durations were not recorded.

Yarmus *et al.* reported aspirated lymph node number per patient as 2.17 in deep sedation group and 1.36 in fentanyl and midazolam group during EBUS-TBNA. The difference between the groups was found statistically significant (14). Steinfort *et al.* evaluated patient satisfaction with conscious sedation during EBUS-TBNA and calculated aspirated lymph nodes per patient as 1.4 (1). In our study, aspirated lymph nodes per patient were detected as 2.21 in midazolam group and 1.33 in propofol + midazolam group. In contrast with the literature, aspirated lymph node number was lower in propofol than the midazolam group. This situation can be explained by increased skill of bronchoscopist during years. While initially EBUS-TBNA were performed under propofol sedation later they were performed under midazolam sedation in our centre.

No significant difference among sedation methods during EBUS-TBNA related to the complications was detected in the literature (11–13, 17). Minor complications during EBUS-TBNA are reported generally, only in the study conducted by Vila *et al.* major complications are reported. Two cases of arrhythmias requiring electrical cardioversion and cardiac compressions were reported in the study comparing sedation with propofol and remifentanil (16). Minor complications such as

temporary desaturation, hypotension, self-restricting bleeding occurred frequently. No major complications were observed in our study and there was no significant difference between the groups in relation to minor complications.

Limitations

The most important limitation of our study is the absence of information about patient and bronchoscopist satisfaction during the EBUS-TBNA procedure. Diagnostic value of the procedures performed with different types of sedation methods is important, however, patient and bronchoscopist satisfaction and procedure duration is as much important.

Strengths

The most important strength of our study is that two different sedation groups that could be seen similar to experimental were formed spontaneously due to the change of sedation policy during EBUS-TBNA procedures in our hospital. Natural randomization occurred. All the EBUS-TBNA procedures were performed by the same two experienced bronchoscopists.

Conclusion

In conclusion, diagnostic efficacy of conscious sedation with midazolam was found similar to sedation with propofol group during EBUS-TBNA. Also the complication rates were similar in both groups. Propofol with midazolam application requires an accompanying anesthesiologist therefore it increases the cost. EBUS-TBNA procedure can be performed under conscious sedation without any decrease in diagnostic yield.

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