Comparison of Moderate versus Deep Sedation for Endobronchial Ultrasound Transbronchial Needle Aspiration

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Abstract

Rationale: Most bronchoscopic procedures are performed using moderate sedation achieved by combining a short-acting benzodiazepine with an opioid agent. Propofol (2,6-diisopropylphenol), a short-acting hypnotic agent, has been increasingly used to provide deep sedation in the endoscopy community with an acceptable safety profile.

Objectives: To compare the impact of moderate versus deep sedation on the adequacy and diagnostic yield of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA).

Methods: A retrospective review of prospectively collected data was performed at two academic institutions with interventional pulmonary fellowships using two methods of sedation during EBUS (deep vs. moderate sedation). Rapid on-site cytologic evaluation was used on all procedures in both groups. EBUS-TBNA nodal sampling was considered adequate if the aspirate yielded a specific diagnosis or lymphocytes. EBUS-TBNA was considered diagnostic if a lymph

node aspirate yielded a specific diagnosis or if subsequent surgical sampling or prolonged radiographic surveillance revealed no nodal pathology.

Measurements and Main Results: No difference was observed in the indication for EBUS-TBNA between the two groups. More lymph nodes were sampled per patient in the deep sedation group (314 nodes from 163 patients; 2.2 nodes per patient) than in the moderate sedation group (181 lymph nodes from 146 patients; 1.4 nodes per patient; $P < 0.01$). The EBUS-TBNA diagnostic yield was higher for the deep sedation group (80% of patients) than for the moderate sedation group (66% of patients; $P < 0.01$).

Conclusions: Diagnostic yield and number of lymph nodes sampled using deep sedation is superior to moderate sedation in patients undergoing EBUS-TBNA. Prospective studies accounting for other factors including patient selection and cost are needed.

Keywords: interventional pulmonology; endobronchial ultrasound; TBNA

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In the United States, the majority of bronchoscopic procedures are performed using moderate sedation achieved by combining a short-acting benzodiazepine

with an opioid agent (1). The sedative and amnestic properties of the short-acting benzodiazepines in combination with the antitussive and analgesic properties of

opioids have been shown to be effective in providing adequate levels of moderate sedation (1). In a recent study of over 300 bronchoscopies performed at four major

academic interventional pulmonary (IP) centers, 92% of the centers used moderate sedation (2). Propofol (2,6-diisopropylphenol), a short-acting hypnotic agent, has been increasingly used to provide deep sedation in the endoscopy community with an acceptable safety profile (3, 4).

In recent years, the diagnostic utility of bronchoscopy has been extended with the addition of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). Routinely, multiple needle passes are taken at several nodal stations to evaluate and stage the mediastinum. This practice, along with the use of rapid on-site cytopathology and the current need to obtain sufficient tissue for molecular analysis, can result in increased procedural times and the need for prolonged anesthesia time (5).

There are no published studies comparing types of sedation with procedural outcomes with EBUS. Importantly, there are no comparative trials that associate levels of sedation during EBUS with differences in diagnostic yield or sample adequacy. We performed this study as a retrospective review of two academic Interventional Pulmonary (IP) programs to determine if a difference in specimen adequacy and diagnostic yield during EBUS-TBNA is associated with different levels of procedural sedation. At one institution, all procedures were performed under intravenous boluses of fentanyl and midazolam administered by a nurse (moderate sedation). At the other institution, all procedures were performed under a continuous infusion of propofol administered by anesthesiologist or a registered nurse anesthetist supervised by anesthesiologist (deep sedation). We found important differences in the number of lymph nodes sampled and the diagnostic yield for EBUS-TBNA favoring the group that received deep sedation.

Methods

The study protocol was approved by the Institutional Review Boards at both institutions (Johns Hopkins University: NA_00041268; University of Pennsylvania: HM13206). A retrospective review of all patients undergoing EBUS-TBNA from January 2009 until December 2009 was performed at the Johns Hopkins Hospital and the Hospital of the University of

Pennsylvania (HUP). All patients with cytopathologic data who underwent EBUS were included, and there were no exclusion criteria. Both academic institutions offer an IP fellowship that provides an additional year of advanced diagnostic and therapeutic training in pulmonary procedures after completion of an accredited Pulmonary and Critical Care fellowship (6).

All EBUS-TBNA procedures were performed together by the IP attending and IP fellow at each institution, who were at the same level and timing of training. Both IP fellows had previously completed 50 EBUS procedures as recommended by the American College of Chest Physician (ACCP) guidelines before study enrollment (6). Each bronchoscopist evaluated and obtained consent from the patient before anesthesia induction. Sedation practice during EBUS was institutional and practitioner dependent. All EBUS procedures at the Johns Hopkins Hospital were performed with deep sedation using propofol as defined by the ASA as described above. A board-certified anesthesiologist or certified registered nurse anesthetist independently assessed each patient before sedation, and sedation was induced with propofol before placement of a laryngeal mask airway or endotracheal tube. The EBUS scope was advanced, and 1% lidocaine was used for topical anesthesia. IP physicians at the Hospital of the University of Pennsylvania performed EBUS with moderate sedation as defined by the ASA. Local anesthesia of the upper airway with 1% lidocaine was administered to all patients' by the IP fellow before insertion of the EBUS scope orally. Moderate sedation was induced with midazolam and fentanyl boluses administered by a registered nurse during the procedure; these medications were managed by the operating physician. During both modalities of sedation, continuous electrocardiographic rhythm monitoring, pulse oximetry, respiratory rate, and intermittent blood pressure monitoring were performed throughout the procedure. All cardiopulmonary activity was recorded by the anesthesiologist, by the certified registered nurse anesthetist, or by the registered nurse administering sedation. After the procedure, all patients were brought to the endoscopy recovery unit for postprocedure monitoring.

Rapid on-site cytologic evaluation (ROSE) was used with all study patients in both study centers. Additionally, both centers used the same dry smear technique

for specimen processing and evaluation. Specimen adequacy of EBUS-TBNA was determined by a lymph node aspiration showing lymphocytes or yielding a specific diagnosis during ROSE. As per general practice, three passes per lymph node were attempted before moving to another nodal station or terminating the procedure (7). A diagnostic TBNA was defined as a lymph node aspiration showing a specific diagnosis (carcinoma, granuloma, etc.) or confirmation of a true negative by mediastinoscopy, surgical resection, or follow-up CT or CT/PET imaging demonstrating resolution or stability of the underlying process that prompted the initial bronchoscopy for 2 years.

Statistical Analysis

Procedure characteristics were evaluated using the chi-squared and Fisher's exact test for binary outcome and the Student's *t* test where appropriate. Univariate analysis of sedation method, sample adequacy, and diagnostic yield were summarized using means $\pm$ SD for continuous variables and proportions for categorical variables. Logistic regression models were created to assess the relationship between diagnostic yield and sedation type. Procedure time, number of lymph nodes sampled, and size of lymph nodes samples were included in the models as potential confounders of this relationship. Additional variables that were significantly associated with diagnostic yield in univariable analyses, defined as a *P* value < 0.10 , were included in a multivariable model. The final model generated included size of lymph nodes, procedure time, and indication for procedure. Goodness-of-fit testing using Pearson's chi-square was performed given the few unique covariate patterns relative to the sample size. Similar analyses were performed in the cohort of patients with carcinoma or lymphoma and in those who underwent PET scans to determine if the indication for EBUS or the presence of positive PET scan influenced the relationship between type of sedation and yield.

In all regression models, multicollinearity was assessed using variance inflation factors and addressed, when necessary, by omitting or recategorizing collinear variables. We defined statistical significance as a two-sided *P* < 0.05 . All analyses were performed

using STATA version 11.2 (STATA, College Station, TX).

Results

During the 12 months of data collection, EBUS-TBNA was performed on 146 patients in the moderate sedation group and on 163 patients in the deep sedation group. ROSE was used on all samples in both groups. Although there was no significant difference in the indication for EBUS-TBNA between groups, there was a trend toward this, likely related to the higher proportion of patients with presumed carcinomas in the moderate sedation group (84.9 vs. 74.9%; $P = 0.13$) (Table 1). A minority of patients had preprocedure PET scans (43.1% in the moderate sedation group vs. 46.6% in the deep sedation group; $P = \text{NS}$), and relatively few were positive, without

a significant difference in proportion between groups.

Procedural-Related Measures

Total procedure time in the moderate sedation group was 46.9 minutes, whereas total procedure time in the deep sedation group was only 36.4 minutes ($P < 0.01$). On average, patients in the deep sedation group had significantly more lymph nodes sampled per procedure than those in the moderate sedation group (2.17 ± 0.97 vs. 1.36 ± 0.63 ; $P < 0.01$) (Figure 1). The total number of passes during TBNA was higher in the deep sedation group only for the first lymph node sampled than in those in the moderate sedation group (3.7 vs. 3.0; $P < 0.01$); there were no differences in the number of passes for the second lymph node sampled (3.0 vs. 2.9; $P = 0.72$). Differences in lymph node sampling locations were not seen between the two

groups when grouped by mediastinal (2, 3, 4, and 7) or hilar (10, 11, and 12) node classification (Figure 2).

All patients in the moderate sedation group received a combination of fentanyl and midazolam intravenously for sedation. The mean dose of midazolam was 6.5 ± 3.4 mg, and the mean dose of fentanyl was 155 ± 52 μg , consistent with prior reports of mean doses required to achieve moderate sedation in other populations (8). All patients in the deep sedation group received an intravenous propofol infusion, and thus total dose received was not recorded.

Complications

Only eight complications related to EBUS-TBNA were found. Seven patients experienced minor bleeding complications, defined as bleeding requiring minimal suction to clear the endoscopic view. One patient developed

Table 1. Procedure characteristics

Variable	Deep Sedation (n = 163 patients, 314 lymph nodes)	Moderate Sedation (n=146 patients, 181 lymph nodes)	P Value*
Preprocedure Indication			0.13
Carcinoma	122 (74.9) [†]	124 (84.9)	
Infectious	7 (4.3)	2 (1.4)	
Lymphoma	9 (5.5)	6 (4.1)	
Sarcoidosis	25 (15.3)	14 (9.6)	
Preprocedure PET scan			0.31
Total	76	63	
Positive	12 (15.8)	16 (25.4)	
Postprocedure Pathology Results			<0.01
Small cell lung cancer	8 (4.9)	3 (2.1)	
Non-small cell lung cancer	60 (36.8)	74 (50.7)	
Lymphoma	10 (6.1)	5 (3.4)	
Sarcoidosis/other granuloma	22 (13.5)	6 (4.1)	
Other cancer	19 (11.7)	5 (3.4)	
Infection	6 (3.7)	0 (0.0)	
Nondiagnostic/normal	37 (22.7)	53 (36.3)	
Number of lymph nodes sampled			<0.01
Per patient (mean $\pm$ SD)	2.2 (0.9)	1.4 (0.6)	
Diameter of first lymph node, cm	1.2 (0.8)	1.8 (1.1)	<0.01
Lymph node stations sampled			<0.01
Total lymph nodes	314 (100)	181 (100)	
2R	7 (2.2)	5 (2.8)	
2L	0 (0)	2 (1.1)	
3R	2 (0.6)	0 (0)	
4R	113 (36.2)	57 (31.5)	
4L	35 (11.2)	8 (4.4)	
7	55 (17.6)	63 (34.8)	
10R	7 (2.8)	11 (6.1)	
10L	9 (2.9)	16 (8.8)	
11R	36 (11.5)	15 (8.2)	
11L	37 (11.8)	11 (6.1)	
12R	12 (3.8)	3 (1.7)	
12L	1 (0.3)	0 (0)	

*P values calculated using Fisher's exact and chi-squared tests for categorical variables and Student's *t* tests for continuous variables.

[†]Data presented as n (%) unless otherwise noted.

Figure 1. Total number of lymph nodes (LN) sampled grouped by number of LN sequentially sampled during endobronchial ultrasound-guided transbronchial needle aspiration.

rapidly reversible hypoxia. No pneumothorax was reported in either group, and no escalation of care was required after any procedure. No significant differences in the incidence or type of complications from EBUS-TBNA were noted between groups.

Adequacy of Sample, Diagnosis, and Diagnostic Yield

Only a minority of procedures was limited by inadequate sample procurement, defined as failure to demonstrate lymphocytes or to yield a specific diagnosis on lymph node aspirate. About 4% ($n = 6$) of the moderate sedation group experienced this outcome,

compared with 1% ($n = 2$) in the deep sedation group ($P = 0.11$). A diagnosis was established in 227 of 309 subjects overall (73.5%), consisting predominantly of malignancy. There were significant differences in the postprocedure diagnoses and in the proportion of patients with nondiagnostic or normal findings between groups, with a higher proportion of the moderate sedation group demonstrating normal or nondiagnostic findings (36.3 vs. 22.7%, respectively). A higher proportion of patients in the deep sedation group underwent mediastinoscopy (15.9 vs. 4.8%, respectively) or had radiographic follow-up

to confirm true-negative status (7.3 vs. 0%, respectively).

Diagnostic yield was significantly higher in the deep sedation group compared with the moderate sedation group, with 130 of 163 (79.8%) versus 97 of 146 (66.4%) of procedures establishing a diagnosis ($P < 0.01$) (Figure 3). Bivariable analyses identified significant associations between procedure time, size of lymph nodes, and indication for procedure and diagnostic yield; other variables were not significantly associated with the outcome. Before adjusting for potential confounders, patients in the deep sedation group were significantly more likely to have a diagnosis established by EBUS-TBNA, with an odds ratio (OR) of 1.99 (95% confidence interval [CI], 1.19–3.33; $P < 0.01$). When controlling for procedure time, size of lymph nodes, and indication for procedure, patients who underwent deep sedation were over 2 times more likely to have a diagnosis established (OR, 2.25; 95% CI, 1.07–4.75; $P = 0.03$). Goodness-of-fit testing indicated a good fit with this model (Pearson's χ^2 ; $P = 0.51$).

Subgroup analyses in the cohort of patients with malignancy (OR, 8.68; 95% CI, 2.94–25.6; $P < 0.01$) and those who had undergone PET scans (OR, 3.82; 95% CI, 1.35–10.87; $P = 0.01$) demonstrated a strong effect of sedation type on diagnostic yield, though larger CIs reflect the smaller number of patients included in each analysis.

Figure 2. Percent of total lymph nodes sampled comparing deep to moderate sedation groups by mediastinal versus hilar lymph node stations. P value shown ($P < 0.05$).

Figure 3. Percent diagnostic yield comparing deep to moderate sedation. *P* value shown ($P < 0.05$).

Discussion

We report the first study directly comparing the diagnostic yield and specimen adequacy of EBUS-TBNA under moderate versus deep sedation for the evaluation of mediastinal and/or hilar adenopathy. In our cohort, the use of deep sedation for EBUS-TBNA was associated with an increase in number of sites sampled per procedure and diagnostic yield when compared with the use of moderate sedation.

Although the use of deep sedation has not been well studied in bronchoscopy, there are studies of note within the gastroenterology literature. Wang and colleagues published a retrospective review of colonoscopies performed with moderate sedation or deep sedation (9). Although the vast majority of procedures were performed using moderate sedation (97%), the authors were able to demonstrate that deep sedation allowed identification of more advanced lesions. They also noted that centers using deep sedation were significantly more successful at identifying advanced lesions.

Deep sedation using propofol has been evaluated for its use in bronchoscopy. However, many of these studies concentrate on safety and sedation performance, not on procedural diagnostic effect (8, 10). Sarkiss and colleagues described the use of total intravenous anesthesia, using propofol and intermittent neuromuscular blockade for the performance of EBUS-TBNA (11). They had no major complications or hospital admissions in over 200 outpatients undergoing EBUS-TBNA. No data regarding diagnostic yield and/or sample adequacy were included in this report.

A number of organizations have provided guidelines for the performance of bronchoscopic procedures, including EBUS-TBNA. Most of these guidelines offer general recommendations about performing the procedure but do not provide information on how to best increase one's diagnostic yield.

The British Thoracic Society (BTS) offers two level B evidence comments within their guidelines (12, 13). The BTS recommends the use of sedation for all patients undergoing bronchoscopy unless contraindicated and the use 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 the use of sedation will most likely allow for easier procedural performance.

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 versus deep sedation were addressed (14).

A recent publication from the ACCP's Quality Improvement Registry prospectively evaluated procedure-specific morbidity, mortality, and diagnostic yield in four tertiary care centers performing advanced diagnostic bronchoscopy procedures (15). A total of 310 procedures were identified, of which 56% were EBUS-TBNA ($n = 173$). The majority of patients received moderate sedation (92%), and only a few received deep sedation (3%) or general anesthesia

(5%). A total of 198 TBNA (25 cases without ultrasound guidance) cases were performed, with nodal sampling confirmed in 82.3% and a diagnostic yield of only 43%.

Deep sedation during gastrointestinal endoscopy is associated with greater patient cooperation, shorter recovery and discharge periods, and higher postanesthesia recovery scores (16). Previous studies have shown that EBUS provides a safe, accurate, and cost-effective method for the diagnosis and staging of lung cancer (17). A portion of the cost savings attributable to EBUS is related to the fact that patients undergoing EBUS may be able to forgo more costly procedures, such as mediastinoscopy (18).

Our study shows that, despite shorter procedure times, deep sedation during EBUS-TBNA allowed for more lymph nodes to be sampled and for more needle passes per site, resulting in improved overall diagnostic yield. We speculate that deep sedation improves patient cooperation, allowing the bronchoscopist to perform more passes per node and sample more nodes per procedure in a shorter timer period, resulting in an improved diagnostic yield. In our diagnostic sampling, there was no difference in the location of lymph nodes stations sampled (i.e., mediastinal vs. hilar) between sedation groups, and procedure experience was similar within the two groups.

There are several limitations to this study. Although this study was performed at different institutions, both are centers of excellence, and the attending IP physicians performing the procedures are experts in EBUS. In addition, the IP fellows participating in the study were at comparable training levels throughout the study, and the volume at each center was similar. The primary indications for patients undergoing EBUS-TBNA were similar in both groups, which suggests that the two patient subsets were similar. The study design is retrospective, although the study compared two groups during the same time period with similar indications for bronchoscopy and proceduralist expertise. A prospective randomized trial comparing these two groups would provide additional compelling data. However, given the trend in institutional preference and anesthesiology availability, this may be difficult to achieve. Another limitation of the study design was the inability to follow up for all true negatives due to incomplete

records and missed patient appointments. There was no difference in lost-to-follow-up data between the two groups. For research equipoise, if pathologic diagnostic data were unavailable, the procedure in question was considered a nondiagnostic bronchoscopy. However, all patients in both groups with a nondiagnostic EBUS who were referred for mediastinoscopy, surgical resection, or 2 years of radiographic surveillance were included in the data analysis.

Because the ROSE technique for specimen preparation was similar between the two groups, we could not consider specimen processing as a potential limiting factor.

In conclusion, deep sedation appears to be superior to moderate sedation during EBUS bronchoscopy. This is the first study to directly compare moderate versus deep sedation during EBUS bronchoscopy in the literature as a primary aim. We believe that increased diagnostic yield using

deep sedation results from the ability to target and sample more lymph nodes in a shorter time. Additional research examining the efficacy of this approach would be valuable. Prospective, randomized trials of varying modes of anesthesia for EBUS will be crucial in answering these questions more definitively. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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