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Deep sedation *versus* minimal sedation during endobronchial ultrasound transbronchial needle aspiration

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Abstract

The sedation plays an important role in the endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) procedure. The sedation can be Minimal (anxiolysis), Moderate (conscious sedation) or Deep. The ACCP guidelines suggest that moderate or deep sedation (DS) is an acceptable approach. In fact, several studies compare moderate *versus* deep sedation, but no study has been carried out to compare deep sedation *versus* minimal. We carried out a retrospective study to compare the Deep *versus* Minimal sedation (MiS) in patients undergoing EBUS-TBNA. The primary end point was the diagnostic accuracy. The secondary end points were adequacy and sensitivity. We evaluated the LN size sampling, procedural time, complications and patient tolerance. Thirty-six patients underwent EBUS-TBNA, 16 under DS and 20 under MiS. The overall diagnostic accuracy for correct diagnosis was 92.9% in DS group and 94.1% in MiS group (p=0.554). Sample adequacy, defined as the percentage of patients with a specific diagnosis by EBUS-TBNA, was 87.5% (14 of 16) and 85% (17 of 20) for the DS group and MiS group, respectively, (p=0.788); the sensitivity was 92.9% in the DS group (95% CI, 73-100%) and 92.9% in the MiS group (95% CI, 77-100%) (p=0.463). There were no major complications in either group. Minor complications were 4 in MiS and 1 in DS (p=0.355). The patients in the MiS group recalled the procedure more often compared to the other group (p=0.041). The majority of the patients would agree to undergo the same procedure again in the future in both groups (p=0.766). In our experience EBUS-TBNA performed under MiS has comparable accuracy, adequacy, sensitivity, complications and patient satisfaction to DS, even if the sample was small. Future prospective multicenter studies are needed to confirm our results.

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Introduction

Endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) has become a standard procedure in diagnosis and staging of lung cancer [1]. EBUS-TBNA is also recommended in patients with suspected sarcoidosis or tuberculosis with mediastinal and/or hilar adenopathy and is suggested in patients with suspected lymphoma [2]. The sedation represents an important step in EBUS-TBNA procedures because the ultrasonitabc bronchoscope has a diameter larger than the conventional bronchoscope and it is necessary to have an intense contact with the bronchial wall to obtain ultrasonic images. Moreover, the sedation is important to prevent reflex coughing and laryngospasm, so as to reduce movements and allow needle insertion more safely reducing the possibility of bleeding by involving a vessel [3]. In fact, an optimal sedation confers a comfortable environment for the patient and at the same time for the bronchoscopist permitting to obtain adequate tissue [4].

The guidelines define the sedation as a continuum of altered consciousness. The types of sedation include minimal sedation (anxiolysis), moderate sedation (conscious sedation), deep sedation, and general anesthesia [2]. Deep Sedation (DS) was defined as a drug-induced depression of consciousness during which patients cannot be easily aroused but respond to repeated or painful stimulation, with potential impairment of independent ventilation and potential need for an artificial airway [5]. DS is administered using a combination of Propofol and Fentanyl and requires anesthesiologist in the bronchoscopy room. Propofol is a rapid–acting sedative that allows quick recovery. This sedation has an amnestic and antiemetic effects but has not analgesic activity [6]. Moderate Sedation (MS) is a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, spontaneous ventilation is adequate and cardiovascular function is usually maintained [5]. MS is mostly preferred method for procedures which requires rapid recovery. This sedation uses a combination of Fentanyl and Midazolam. Midazolam is a benzodiazepine with a rapid-onset and short duration, for this reason it is the benzodiazepine of choice in this type of procedure [7]. Fentanyl is a preferred opioid [4] because it has high potency, fast onset of action, few adverse events, synergy with benzodiazepines and it is cleared rap-

idly [8]. Meperidine can be used in short procedures for MS because it is a short-acting opioid narcotic with a half-life of 3.2 h [9,10].

Minimal Sedation (MiS) is a drug-induced state during which patients respond normally to verbal commands. Although cognitive function and physical coordination may be impaired, airway reflexes, and ventilatory and cardiovascular functions are unaffected [5]. MiS is also defined anxiolysis and provides the administration of only Midazolam.

In literature, there are several studies that compare Deep Sedation *versus* Moderate Sedation, but, to our knowledge, there are no studies that compare Minimal *versus* Deep Sedation. The aim of this study was compared EBUS-TBNA performed under Deep Sedation *versus* Minimal Sedation.

Materials and Methods

The study was a retrospective and observational study conducted at the Pulmonary Disease Unit of Azienda Ospedaliera ULSS 2 Marca Trevigiana Distretto Vittorio Veneto between September 2016 and July 2017. The study was approved by the Institutional Ethics Committee of the Province Treviso and Belluno (Approval N° 2332).

Overall, 36 consecutive patients underwent EBUS-TBNA in Minimal Sedation or Deep Sedation at our hospital for diagnosis of mediastinal/hilar lymphadenopathy or paratracheal/peribronchial mass. Chest TC was mandatory before the procedure and LNs were considered potentially malignant if the short axis diameter was >10 mm. Specifically, we adopted a selective assessment for the staging according to Detterbeck's classification [11].

EBUS transbronchial needle aspiration was performed with a real-time ultrasound bronchoscope (BF-UC-180F; Olympus Ltd., Tokyo, Japan). A 7.5-MHz linear ultrasound transducer with a maximal penetration of 50 mm was linked to a processor (EU-ME1; Olympus Ltd.). Transbronchial needles aspiration were performed with a dedicated 22-gauge needle (NA-201SX; Olympus Ltd.). An experienced operator performed all bronchoscopic procedures in a dedicated suite and no trainees were involved. The sample was always analyzed by the same cytopathologist.

The type of sedation given to patients was random, based on the availability of the anesthetist to be in the endoscopic room, and the choice of sedation was not influenced by the assessment of specific risk factors in both groups. In case the anesthetist was not available, the procedure was made with only Midazolam because the pneumologist could not use Fentanyl due to the hospital's rule.

The patients in DS group received a combination of Propofol and Fentanyl and the support of laryngeal mask on supine position, with the anesthesiologist in the bronchoscopy room. The patients in DS group received, in addition to topical aerosolized 2% lidocaine, a combination of Propofol (1.5-4.5 mg/kg) and Fentanyl (up to 150 µg) in accordance with local hospital sedation policies.

Instead, the patients in MiS group received, in addition to topical aerosolized 2% lidocaine, only Midazolam i.v. on supine position. An initial Midazolam 2.5 mg i.v. bolus was followed by bolus of 1 mg in order to obtain an adequate patient sedation, considering a maximum dosage of 0.1 mg/Kg [12]. Oxygen saturation, ECG, heart rate, blood pressure, vital signs and the thoracic cage excursion were monitored throughout the procedure according to bronchoscopy BTS guidelines [13].

We evaluated baseline patient characteristics, lymph node size (short axis) and location, number of lymph nodes sampled, complications, procedure time, and final cytological, histological diagnoses and immunohistochemical. Then we assessed a patient tolerance with a Likert's scale-type questionnaire provided by phone the day after the procedure. The procedure time was measured from the initial endobronchial-ultrasound (EBUS) bronchoscope insertion by mouth to the final removal of the EBUS bronchoscope. Furthermore, we evaluated the main complications related to the procedure: EBUS-related complications (*i.e.* bleeding, pneumothorax); and sedation-related complications such as hypotension (systolic <90 mm Hg), hypoxemia (oxygen saturation of <90% for >1 min) arrhythmias and excessive coughing that prevented the completing the procedure.

The primary end-point was diagnostic accuracy (DA). The DA of a particular procedure can be expressed in terms of sensitivity and specificity or odds ratio, in according to definition of Reitsma *et al.* [14]. We defined as an accurate procedures the EBUS-TBNA that provided a diagnosis, malignant or not, and we calculated the DA in according to this formula (true positive + true negative)/(true positive + true negative +false positive + false negative).

The secondary end points were sampling adequacy and sensitivity. The sampling adequacy was considered adequate if it presented enough cells to diagnose a specific benign/malignant condition (*i.e.*, diagnosis of cancer, infection or sarcoidosis), or a preponderance of lymphocytes. The inadequate sample was considered a sample with blood, a preponderance of bronchial cells, a minority or no lymphocytes and no features specific to a diagnosis.

The DA and sensitivity were calculated according to the following criteria: the sample was considered as "true positive" when it was possible recognize a specific disease; as "true negative" the sample with lymphocytes confirmed by surgery or 6 months clinical and radiological follow-up by CT demonstrating stability or decrease in the size of the lesion or lymph node; as "false negative" were defined as patients subsequently diagnosed with malignant or other conditions at later investigations (*i.e.*, thoracic surgery, exam repetition) or by radiological follow-up with an increase in the size of lesions or lymph nodes.

The statistical analyses were used to describe the study population. Pearson's chi-squared test (or Fisher's exact test) and *t*-test were used to determine the significance of differences between the study groups. Sensitivity values were provided with the corresponding 95% confidence interval (95% CI). Statistical analysis was performed with PRIMIT statistical software.

Results

Between September 2016 and July 2017, 36 consecutive patients referred for EBUS-TBNA were assessed: 16 patients to the Deep Sedation group and 20 to the Minimal Sedation group. Demographic and baseline clinical characteristics were well balanced:

Sex (in DS group: F 50% M 50%, in MiS F 45%, M 55%) and age (in DS group 66.8 ± 14.6 y, in MiS group 67.7 ± 16.7 y p=0.868) (Table 1). In the MiS group, the average dose of midazolam was 4.4 ± 1.0 mg; in the DS group the average dose of Fentanyl/Propofol were 100 ± 18 µg/250 ± 52 mg.

A total of 24 targets were sampled in the DS group (1.5 ± 0.6 per patient), and 28 targets were sampled in the MiS group (1.4 ± 0.5 per patient) (p=0.599). The diagnostic accuracy was 92.9% in DS group and 94.1% in MiS group (p=0.554). The adequacy of EBUS-TBNA was 87.5% (14 of 16) and 85% (17 of 20) for the DS group and MiS group, respectively, (p=0.788). Malignancy was found in 55% (11 of 20) in the MiS group *versus* 68.8% (11 of 16) in the DS group (p=0.501) (Table 1). The final diagnosis was malignancy in 22 patients (adenocarcinoma, n = 9; squamous cell carcinoma, n = 5; small cell carcinoma, n = 1; NSCLC, n = 3; metastasis, n = 1;) and benign condition in the remaining 9 patients (reactive lymphadenopathy, n = 5; sarcoidosis, n = 3; Tuberculosis, n = 1) (Table 1).

Immunohistochemical studies were obtained for all cases. In particular, the EBUS had a diagnostic purpose in 13 patients (6 in DS group

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and 7 in MiS group) and had a staging aim with selective assessment in 23 patients (10 in DS group and 13 in MiS group) (p=1.00).

The sensitivity of EBUS-TBNA was 92.9% in the DS group (CI 95%, 73%-100%) and 92.9% in the MiS group (CI 95%, 77%-100%) (p=0.463). In the DS group the procedure duration was 24.5 ± 8 minutes (range 11-36) and 23.05 ± 6.82 minutes (range 10-36) in the MiS group (P=0.561) (Table 1). EBUS was completed in all patients in the DS group, and in the MiS group.

There were no major complications or escalation of care related EBUS procedure or type of sedation in either group. Minor complications, reported by medical report, were 4 in MiS group and 1 in DS (p=0.355), in particular excessive amount of cough in 4 patients in MiS group (p=0.113) and hypoxemia in 1 patient in DS group (p=0.444) but the exams were completed in all cases (Table 2).

The results of the questionnaire showed that the patients in the MiS group recalled the procedure more often compared to the other group

Table 1. Baselines characteristics, procedure time, characteristics of limphnodes, and adequacy.

	Deep sedation	Minimal sedation	p
N patients	16	20	
Age			0.868
Mean (SD)	66.8 (14.6)	67.7 (16.7)	
Median	70.5	73	
Min-Max	41-89	27-92	
Sex			0.765
Female	8 (50%)	9 (45%)	
Male	8 (50%)	11 (55%)	
LNs or masses			0.599
n	24	28	
Mean (SD)	1.5 (0.6)	1.4 (0.5)	
LN or mass size (mm/short axis)			0.110
Mean (SD)	21.5 (7,3)	17.6 (7.2)	
Median	20	15.5	
Min-Max	10-40	10-35	
Procedural time (min)			0.561
Mean (SD)	24.5 (8)	23.05 (6.82)	
Median	25	24	
Min-Max	11-36	10-36	
LN stations/masses			
7	6	14	
4R	14	12	
4L	1	1	
10R	2	0	
2R	1	0	
Mass	0	1	
Malignancy	11	11	0.501
Lung, adenocarcinoma	4	5	
Lung, squamous cell	4	1	
Lung, NSCLC	2	1	
Lung, small cell	1	3	
Metastasis	0	1	
Inflammation/infection	3	6	0.700
Sarcoidosis	1	2	
Tuberculosis	1	0	
Reactive lymphadenopathy	1	4	

LN: lymph node; L: left; R: right.

Table 2. Complications during deep and minimal sedation.

	DS	MiS	p
n	1	4	0.355
Hypotension	0	0	
Hypertension	0	0	
Hypoxemia	1	0	0.444
Excessive cough	0	4	0.113
Arrhythmias	0	0	

DS: deep sedation; MiS: minimal sedation.

("small amount": 18.75% in DS and 55% in MiS; "significantly": none in DS and 5% in MiS)(P=0.372) with a statistically significant difference (P=0.041). However, the majority of the patients would agree to undergo the same procedure again in the future in both groups ("definitely would": 62.5% in DS and 40%; "probably would": 25% in DS and 45% in MiS; "unsure": 6.25% in DS and 10% in MiS; "probably not": 6.25% in DS and 5% in MiS) (P=0.766).

The most commonly reported symptoms was cough ("small amount": 37.5% in DS and 45% in MiS; "significantly": none in DS and 10% in MiS) (P=0.327). Other discomfort symptoms were sore throat ("small amount": 25% in DS and 45% in MiS; "significantly": none in DS and none in MiS) (P=0.372) and chest pain ("small amount": 12.5% in DS and 25% in MiS; "significantly": none in DS and none in MiS) (P=0.426).

Discussion

The ideal type of sedation in EBUS procedures is an important question for bronchoscopist because a correct sedation involves the procedure's optimization, increasing the satisfaction of patient, the diagnostic accuracy and reducing complications. Furthermore, the sedation represents a cost of care and a cost in terms of anesthesia services and medications. Usually, the choice of sedation depends on several factors such as the bronchoscopist experience, the availability of the anesthetist and the patient choice.

The ACCP guidelines suggest, in patients undergoing EBUS-TBNA, moderate or deep sedation as an acceptable approach (Grade 2C) [2].

In literature, several studies compared moderate sedation (Midazolam + Fentanyl) and deep sedation (Propofol + Fentanyl). An important review [4] showed the results of all main studies [15-20] present in the literature that compared the Deep Sedation *vs* Moderate Sedation. The studies evaluated: diagnostic yield, lymph node sampling, lymph node size, procedural time, complications and patient satisfaction. The results showed that the Moderate Sedation and the Deep Sedation had no significant differences in diagnostic yield, duration of the procedure, complications and patient's satisfaction [4].

One of these, the study by Casal *et al.* [21] was a prospective study. In this study, at the end of the procedure, a questionnaire was provided to all patients to determine satisfaction and tolerance of the procedure. In this study, there were no significant difference in diagnostic yield, rate of major complications, or patient tolerance of EBUS-TBNA, between both groups. The main limitation of this study was that the procedures were performed in centers with a highly experienced operator [21].

Another study evaluated patient satisfaction in DS or MS: a combination of Midazolam/Fentanyl was given to 13 patients, whereas a combination of Midazolam/Propofol, Fentanyl/Propofol or Midazolam/Fentanyl/Propofol was given to 28 patients. In this study resulted that the satisfaction and tolerance of the patients were independent of the type of sedation, with no significant difference in two groups [22].

Similarly, the study by Agostini *et al*. showed a very high patient satisfaction, a full cough control and a safe procedure with a cost reduction during EBUS-TBNA under conscious sedation using Meperidine and Midazolam [23].

To our knowledge, the present study is the first retrospective study that compared the EBUS-TBNA in Deep Sedation, with anesthetist in endoscopic room, *versus* Minimal Sedation in terms of diagnostic accuracy, adequacy, sensitivity, and patient satisfaction. In literature there is a paucity of studies that evaluated the impact of the sedation technique in terms of diagnostic accuracy for endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA), but reported only the diagnostic yield. In our institute, the pneumologist could not use the combination of fentanyl and midazolam due to the hospital's rules, so without anesthetist in endoscopic room we used MiS technique for EBUS-TBNA.

All the EBUS-TBNA procedures were performed in one center, by only bronchoscopist and the samples was analyzed by the same cytopathologist. This can potentially avoid a multiple confounding factor (different individuals performing procedures, different cytopathologist, *etc*.).

In literature we found one study only that evaluated the diagnostic accuracy for the EBUS-TBNA under Deep Sedation (DS) and Moderate Sedation (MS). Fronzen *et al.* [24] showed that there was no significant difference in diagnostic accuracy for EBUS under DS *versus* MS, 88.5-93.2% and 93.6-95.5% respectively. These results were similarly to our percentages in DS and MiS.

In our study the diagnostic accuracy in DS was 92.9% and the accuracy in Minimal Sedation group was 94.1% showing no significant difference in diagnostic accuracy for EBUS under Minimal Sedation or Deep Sedation. The EBUS-TBNA time resulted shorter for the group in minimal sedation (23.05 min in minimal sedation *vs* 24.5 in deep sedation). This could be explained by the fact that the bronchoscopist performed the procedures more quickly in patients in minimal sedation to lower the risk of movement or cough from the patient.

The complications that we have seen in our study were coughing and hypoxemia. The coughing was more common in MiS group, we registered four cases, however there was no significant difference to DS group. Then we registered a peripheral oxygen desaturation in one case in DS; also in this case there was no significant difference to MiS group. The respiratory depression was controlled by flumazenil and naloxone administration [18,25]. The hypoxemia was a side effect of Propofol and Fentanyl given to DS group. In fact, the main adverse effect of this drugs are respiratory depression, apnea and hypotension [26].

In both groups, the questionnaire highlighted that the EBUS-TBNA in deep sedation and in minimal sedation was associated with a high availability to, eventually, undergo again the procedure, suggesting good tolerance of the procedure. In fact, in our study, we found no significant difference in patient satisfaction between DS group and MiS group, but the patients in the MiS group recalled the procedure more often compared to the other group with a statistically significant difference. The symptoms reported by patients, were not relevant because the majority of the patients would agree to undergo EBUS again.

Although the bronchoscopist prefers to perform the procedure in deep sedation or moderate sedation, according to the guidelines, to reduce the patient's movements and to prevent reflex coughing, in our experience there was not significant difference in accuracy, sample adequacy, sensitivity, time of procedure, and minor complications in minimal sedation group *versus* deep sedation group.

The main limit of our study is the small size of the sample. Moreover, our study has an observational and retrospective design which limits generalizability of the results, but its internal validity sounds quite good because the control group is comparable to the exposed group [27]. Another limit is the expertise of the bronchoscopist. In fact, the EBUS-TBNA procedures was performed by an interventional pulmonologist with a long experience in conventional-TBNA and EBUS-TBNA. The same consideration should be made for the cytopathologist, expert in respiratory cytopathology, that analyzed all the samples.

In conclusion, in this retrospective study, we show that the type of sedation used does not impact the diagnostic accuracy, adequacy, sensitivity and complications of EBUS-TBNA, but the small size of the sample does not allow definitive conclusions to be drawn.

However, we believe that these results are relevant for situations where it is not always possible to have anesthetist in endoscopic room,

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when the EBUS-TBNA, due to institutional rules, cannot be performed in moderate sedation. Patients under MiS recalled the procedure more often to patients under DS but this was not influenced the procedure's satisfaction.

Despite the small size of sample in our study, we consider the minimal sedation a safe procedure and an efficient alternative, when there is a skilled and well-versed nursing and medical team, reducing also the cost of care. The study can be considered a preliminary research and future prospective multicenter studies are needed to confirm our results.

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