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Local Anesthesia Thoracoscopy with versus without Midazolam: A Randomized Controlled Trial

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Abstract
Background: Medical thoracoscopy is the gold standard for the diagnosis of pleural diseases. To date, no consensus exists regarding the choice of sedative and analgesic agents in patients undergoing local anesthetic thoracoscopy (LAT), and questions are raised as to whether sedatives may add to respiratory side effects. ***Objective:*** The aim of the study was to test the hypothesis that administration of midazolam associated with lidocaine versus lidocaine alone in patients with LAT adds to respiratory side effects. ***Methods:*** We randomly assigned 80 patients to a 1:1 study to 2 groups: local anesthesia by lidocaine (n = 40) versus lidocaine and midazolam (n = 40), with the primary end point being the mean lowest oxygen saturation. The secondary end points were cardiovascular parameters, complications, days of drainage, hospital stay, and patients' quality of life (QoL) as assessed by a visual analog scale (VAS). ***Results:*** The mean age of all patients was 66.6 ± 13.1 years. The study comprised 50 males (62.5%). No difference was observed in the demographics between the 2 groups. No significant difference was observed between the 2 groups in oxygen saturation (primary end point). A significant difference was observed in favor of the midazolam group regarding the QoL assessed by VAS. ***Conclusion:*** Midazolam does not add to respiratory side effects when it is used with lidocaine for LAT, while patients' QoL is actually improved in this group. Therefore, in our department, we changed our startegy in favor of the association of lidocaine and midazolam.

Introduction

Medical thoracoscopy (MT) was first performed by the Swedish physician Jacobaeus in 1910 by inserting a cystoscope in the pleural cavity of a patient with tuberculosis

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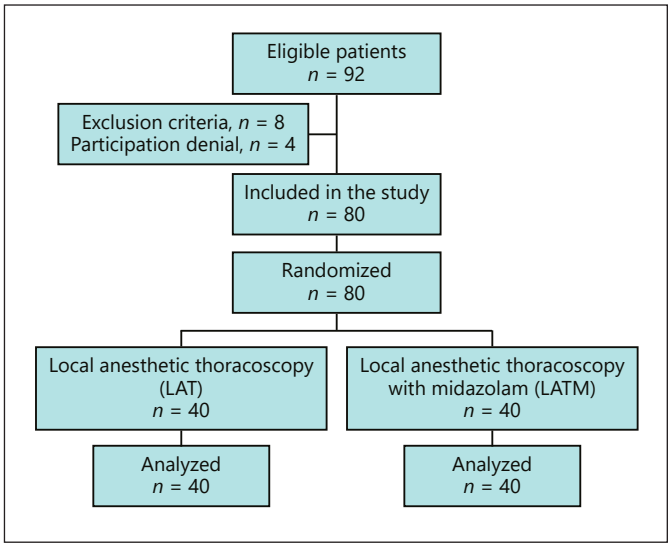

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Fig. 1. Study design.

[1]. Since then, respiratory physicians perform thoracoscopy commonly in order to investigate and treat pleural diseases. In pleural diseases, the diagnostic and therapeutic indications for MT include malignant pleural disease, pleural infections, and pneumothorax [2, 3]. The procedure is performed in the endoscopy suite, under local anesthesia and/or mild sedation, with the patient under spontaneous ventilation, making it safe and ensuring low risk of complications [3].

Currently, no consensus exists regarding the choice of sedative and analgesic agents for patients undergoing MT [4–6]. During the classical technique, local anesthesia is primarily achieved with 1% lidocaine solution before the trocar insertion [3]. Some centers, like ours, use only this technique to perform thoracoscopy. In addition to local anesthesia, some centers use sedative agents [3, 4], such as midazolam, diazepam, or propofol, also utilized in bronchoscopy [7, 8], alone or in association to opioids, such as fentanyl or pethidine, to achieve analgesia [3, 4].

Sedation or anesthesia during endoscopic procedures may increase the risk of complications, with hypoxemia being one of the most significant ones [9] which can lead to myocardial infarction and death [10, 11]. Therefore, in some countries, manipulation of these drugs is performed only in the presence of an anesthesiologist, although thoracoscopy is a minimally invasive technique [4]. Overall, few data report the effects of these drugs in patients undergoing MT; only 2 prospective studies exist: Tschopp and collaborators [5] performed a feasibility and safety study on propofol enrolling 53 patients, and Grendelmeier and collaborators [6] conducted a randomized non-inferiority study comparing midazolam to propofol. Although local anesthesia is the classic method for performing thoracoscopy, it has never been investigated versus any sedative in a control trial to provide clear information on whether the classical method has lower complications and equal quality of life (QoL) parameters in this patient population.

Therefore, this prospective, single-center, randomized, open-label, non-inferiority study was designed to compare the effects of lidocaine with midazolam in patients undergoing MT and to lidocaine alone in terms of complications and tolerance of the procedure.

Materials and Methods

Study Design and Data Collection

The study enrolled patients, after signing an informed consent, with undiagnosed pleural effusion admitted in the Department of Respiratory Medicine of the University Hospital of Alexandroupolis, between July 2014 and October 2017, with indication for MT to either local anesthetic thoracoscopy (LAT) with lidocaine 2% versus thoracoscopy with a combination of lidocaine 2% and an intravenous administration of midazolam (LATM) according to the BTS guidelines [12]. Patients were assessed by a pulmonologist and an anesthesiologist prior to the procedure. A thorough medical history identifying comorbidities, current medications, and physical examination including BMI, electrocardiogram evaluation, blood arterial gases, oxygen saturation, spirometry, and chest X-ray were performed on each patient. The physical status was assessed by the anesthesiologist according to the American Society of Anesthesiologists (ASA) physical status classification system [13]. Following completion of the pre-procedural assessments, eligible patients were randomly assigned to the LAT or LATM group in a 1:1 allocation ratio.

During the mentioned period, 92 consecutive patients were screened and 80 were finally enrolled in the study and assigned to the 2 groups (Fig. 1). The inclusion criteria were patients with an indication for diagnostic or therapeutic MT, aged 18 years or older, and with a physical status equal or lower than ASA = 4 [13]. The exclusion criteria were patients with a known allergy or intolerance to midazolam or lidocaine, those with renal or hepatic impairment, intubated patients, pregnant or breastfeeding women, patients with severe mental disorders that would affect their ability to participate in the study, and patients with a physical status of ASA = 5 or 6. Following the medical evaluation, a patient fulfilling the inclusion criteria with no exclusion criteria was randomly assigned to group LAT or LATM.

The primary end point of this study was the mean lowest oxygen saturation during the procedure. The secondary end points were differences in mean lowest heart rate; systolic and diastolic blood pressure; complications during the procedure, such as uncontrollable cough, hypotension, hemorrhage, transfer to the intensive care unit, and death; days of drainage; hospital stay; need for analgesia during the procedure; QoL by using a visual analog scale (VAS); and mean blood concentrations of lidocaine in both groups and midazolam in the LATM group.

Medical Thoracoscopy

Thoracoscopy was performed in an endoscopy suite with the patient in the lateral decubitus position with the involved side upward by 2 pulmonologists and a nurse trained in endoscopic procedures. All patients were under constant cardiopulmonary monitoring during the procedure. Oxygen supplementation via nasal cannula was provided in a standard basis of 2 L/min for both groups [12]. A 10-mm single incision was performed in the fifth or sixth intercostal space in the midaxillary line following local administration of a 2% lidocaine solution, as indicated for intercostal blockage [14]. A 7-mm trocar was inserted, the pleural fluid was drained, and a rigid 0° telescope was used for inspection of the pleural cavity. A minimum of 10 biopsy samples from the pleura were obtained using optical forceps through the trocar. For therapeutic pleurodesis, a poudrage of 4 g of small particle, asbestos-free sterile talc (STERITALC® Novatech, France) was applied. A 24-French gauge chest tube connected to a multichamber drainage system at 10 cm H_2O negative pressure was inserted at the end of the procedure. The chest tube was removed according to the procedure [12].

In the LATM group, an anesthesiologist was present throughout the procedure. Patients received a slow intravenous infusion of 2 mg 5 min before the procedure, followed by additional doses to maintain adequate sedation as indicated by the ASA, according to the anesthesiologist evaluation with the concern to spontaneously breathing [6, 7, 13, 15]. Analgesics were not administrated as standard but as needed according to the physicians' decision.

Oxygen saturation, heart rate, and blood pressure were recorded at the beginning of the procedure (T0), at 15 min (T15), and at the end of the procedure (Tend). After the end of the procedure, the patient was asked to rate the procedure for cough and pain using a VAS from 0 to 100 mm [7], with 0 indicating not present and 100 highly present. The same scale was used 24 h after the procedure to rate discomfort, fear, and willingness to repeat the procedure (for willigness: 0 is extremely willing and 100 not willing at all). Chest X-rays were performed routinely before, immediately after the procedure at the drain removal, and upon discharge.

Pharmacokinetics of Lidocaine and Midazolam

Sample Extraction Procedure

Blood samples were obtained from a peripheral vein for lidocaine 2% at time = 30 min to determine maximum concentration in both groups [16]. The same sample from the midazolam group was used to measure the midazolam blood concentration, as no comparison was possible and the blood concentration of the drug remains still up to 60% of the maximum concentration [17], avoiding multiple blood sampling which might render the procedure quite physically draining for the patient. The samples were immediately centrifuged at 2,000 *g* for 10 min, and the resulting plasma samples were harvested and stored at −80°C pending analysis. The analysis of target compounds (lidocaine and midazolam) in the plasma samples was performed following previously described methods [18] with some modifications. Solid-phase extraction procedure was performed with LiChrolut EN (200 mg, 3 mL). Plasma (1 mL) was diluted with PBS (pH 7.0, 1 mL) before loading onto a cartridge. Before the sample loading, the cartridge was conditioned with 1 mL of methanol. The cartridge was then washed with 2% ammonium hydroxide in a 10% methanol solution (1 mL) and dried for 2 min. Target compounds were then eluted using 3 mL of methanol with 1% formic acid. The eluate was evaporated until dry under a gentle stream of nitrogen and then reconstituted into 1 mL of methanol: water (90:10). Prior to chromatographic analysis, the samples were filtered through syringe-driven membrane filters (PTFE, 0.45 μm) and transferred to screw cap vials for subsequent injection in the LC-LTQ/Orbitrap MS.

Instrumentation

The analysis was performed using an ESI-LTQ-ORBITRAP XL unit (Thermo Scientific, Bremen, Germany) coupled with an Accela 600 pump and Accela autosampler. The Orbitrap unit was operated in positive mode, with a spray voltage of 3.6 kV, while the sheath gas flow rate and auxiliary gas flow rate were adjusted to 38 and 15 arbitrary units, respectively. The capillary voltage and the tube lens voltage were set to 50 and 80 V, respectively. The scan ranged from 150 up to 1,000 m/z. For the fragmentation study, a data-dependent scan was performed. The normalized collision energy of the collision-induced dissociation was set to 35 eV. Separations were performed on a SpeedCore Diphenyl C18 column, 50 × 2.1 mm, 2.6 μm (Fortis Technologies Ltd). The mobile phase consisted of (A) 0.1% formic acid in water and (B) 0.1% formic acid in methanol. The gradient was as follows: 0 min: 95% A, 0–3 min: 30% A, 3–6 min: 0% A, 6–9.10 min: 95% A, and 9.10–10 min: 95% A. The flow rate was 400 μL/min, and the injection volume was 5 μL. Data processing for high-resolution MS (60,000) and MS^2 (30,000) was carried out using Xcalibur software 2.1.0 by Thermo Scientific.

Statistical Analysis

This is a randomized, non-inferiority study designed to meet all quality criteria [19]. The sample size was calculated for a 2-sided significance, a level of 0.05 and a power of 0.8 [20]. Considering that the mean oxygen saturation for midazolam was 96% with a SD of 3% in a previous randomized study [6] comparing midazolam to propofol in the same field, to detect a significant difference between the 2 groups, the minimum sample size was 35 patients per group, and considering 5% of failure, this sample size became 39. We included 40 patients in each

Table 1. Demographic characteristics of our population according to the groups: LAT and LATM

	Total (n = 80)	LAT (n = 40)	LATM (n = 40)	p value
Age, years	66.6±13.1	67.4±11.7	65.8±14.4	0.58
Male gender, n (%)	50 (62.5)	25 (62.5)	25 (62.5)	
BMI, kg/m^2	27.7±5.5	28.2±5.8	27.1±5.1	0.37
Smoking, n (%)				
Nonsmoker	29 (36.3)	16 (40)	13 (32.5)	0.49
Ex-smoker	21 (26.2)	10 (25)	11 (27.5)	
Current	30 (37.5)	14 (35)	16 (40)	
ASA, n (%)				
Class I	14 (17.5)	6 (15)	8 (20)	1.3
Class II	22 (27.5)	10 (25)	12 (30)	
Class III	31 (38.7)	18 (45)	13 (32.5)	
Class IV	13 (16.3)	6 (15)	7 (17.5)	
Indication, n (%)				
Diagnostic	68 (85)	33 (82.5)	35 (87.5)	0.53
Therapeutic	12 (15)	7 (17.5)	5 (12.5)	
Diagnosis, n (%)				
Malignant effusion	51 (63.7)	27 (67.5)	24 (60)	0.64
Nonmalignant effusion	29 (36.3)	13 (32.5)	16 (40)	

ASA, American Society of Anesthesiologists; LAT, local anesthetic thoracoscopy; LATM, local anesthetic thoracoscopy with midazolam.

group. Every patient's assignment was carried out in the waiting room of the bronchoscopy suite by a research nurse. Randomization was through arbitrary allocation to one of the 2 treatment groups based on a computer-generated random list [6].

The mean values and SD were calculated for continuous data in both groups. Normally distributed data were compared between the 2 studied groups using the Student t test for means equality. ANOVA was used to evaluate differences in repeated measurements in the same group of patients. Fischer's exact test was used to determine differences in nominal variables. Simple regression analysis was used to assess the relationship between variables. A p value of <0.05 was considered statistically significant. We used a statistical software package (Stat View®, version 4.5; Abacus Concepts Inc., Berkeley, CA, USA) for the statistical analysis of our data.

Results

The 2 groups were equally matched as shown by their demographic characteristics in Table 1. An indication for MT was in 85% of cases for diagnostic purpose and in the remaining 15% for therapeutic purpose (Table 1). Detailed diagnoses are presented in Table 2.

Table 2. Detailed diagnosis of our patient population (n = 80)

Malignant diagnosis	51 (63.7%)
Lung carcinoma	24 (30%)
Adenocarcinoma	15 (18.7%)
Squamous cell carcinoma	3 (3.7%)
Large cell neuroendocrine carcinoma	2 (2.5%)
Small-cell carcinoma	4 (5%)
Mesothelioma	10 (12.5%)
Genital tract carcinoma	5 (6.2%)
Breast carcinoma	4 (5%)
Adenocarcinoma of unknown primary	4 (5%)
Non-Hodgkin lymphoma	1 (1.2%)
Thyroid carcinoma	1 (1.2%)
Parotid adenocarcinoma	1 (1.2%)
Epitheloid hemangioendothelioma	1 (1.2%)
Nonmalignant diagnosis	29 (36.2%)
Nonspecific pleuritis	19 (23.7%)
Empyema	5 (6.2%)
Eosinophilic pleuritis	2 (2.5%)
Tuberculous pleuritis	2 (2.5%)
Lupus-associated pleuritis	1 (1.2%)
Total	80 (100%)

Primary End Point

There was no statistically significant difference regarding oxygen saturation between the 2 groups at any time points. Oxygen saturation was equally decreased

Table 3. Parameters studied according to the groups: LAT and LATM

Parameter	LAT (n = 40)	LATM (n = 40)	p value
Sedation			
Lidocaine, mg	308.7±59.9	323.5±96.1	0.41
Midazolam, mg	–	2.3±0.7	
Duration, min	23.2±6.1	24.3±5.1	0.41
Oxygen saturation (SaO_2), %			
Beginning of the procedure (T0)	98.1±1.6	98.3±1.8	0.60
15 min in the procedure (T15)	97.3±2	97.7±2.7	0.46
End of the procedure (Tend)	96.8±1.9	98.1±2.1	0.060
Lowest saturation during the procedure	96.4±2.1	97.1±2.6	0.19
Change at 15 min	−0.8±1.5	−0.4±2.2	0.35
Change at end	−1.2±1.6	−0.15±1.9	0.078
Lowest	−1.67±2.1	−1.1±1.9	0.25
Heart rate, beats/min			
Beginning of the procedure (T0)	89.6±14.9	82.7±13.6	0.34
15 min in the procedure (T15)	88.7±16	78.5±14.1	0.035
End of the procedure (Tend)	88.9±15.2	78.7±13.7	0.025
Lowest HR during the procedure	85.7±15.4	76.4±13.9	0.060
Change at 15 min	−0.9±7.6	−4.1±8.1	0.078
Change at end	−1.6±2.1	−4.3±2.1	0.064
Lowest	−3.7±5.8	−6.2±8.1	0.11
SAP, mm Hg			
Beginning of the procedure (T0)	140±16.1	138.3±19	0.61
15 min in the procedure (T15)	133±21.9	123.8±23.4	0.073
End of the procedure (Tend)	134.8±19.2	124.3±22	0.42
Lowest BP during the procedure	128.7±21.7	120.2±20.1	0.69
Change at 15 min	−6.4±15.8	−14.2±20.1	0.057
Change at end	−5.7±14.7	−13.5±18.7	0.042
Lowest	−11.8±13	−17.8±16	0.069
Diastolic blood pressure, mm Hg			
Beginning of the procedure (T0)	73.9±13.5	74.8±15.5	0.78
15 min in the procedure (T15)	72.6±13.3	67.7±16.7	0.15
End of the procedure (Tend)	73.1±12.2	68.9±15.8	0.93
Lowest pressure during the procedure	66.9±12.3	63.8±16.1	0.17
Change at 15 min	−1.5±13.6	−7.2±17.7	0.11
Change at end	−1.1±13	−6.5±15.2	0.093
Lowest	−6.9±8.9	−10.7±15.5	0.17
Complications, n (%)			
Uncontrollable cough	1 (2.5)	0 (0)	0.85
Hypoxemia, SaO_2 <90%	1 (2.5)	1 (2.5)	0.15
Hypotension, SAP <90 mm Hg	2 (5)	3 (7.5)	0.88
Bradycardia, <60 beats/min	0 (0)	3 (7.5)	0.08
Pain necessitating treatment	1 (2.5)	0 (0)	0.85
Days of drainage	2±1.4	2.22±1.9	0.66
Hospital stay	6.6±4.7	6.2±4.9	0.65

mm Hg, millimeter of mercury; LAT, local anesthetic thoracoscopy; LATM, local anesthetic thoracoscopy with midazolam; SAP, systolic arterial pressure.

in both groups at T15 min of the procedure (97.3 ± 2 in the LAT group vs. 97.7 ± 2.7 in the LATM group, p = 0.46) and at the end of the procedure as well (96.8 ± 1.9 in the LAT group vs. 98.1 ± 2.1 in the LATM group, p = 0.06). Overall, 2 patients (2.5%) experienced a drop in SaO_2 to below 90% (88 and 89%), 1 in each group (Table 3).

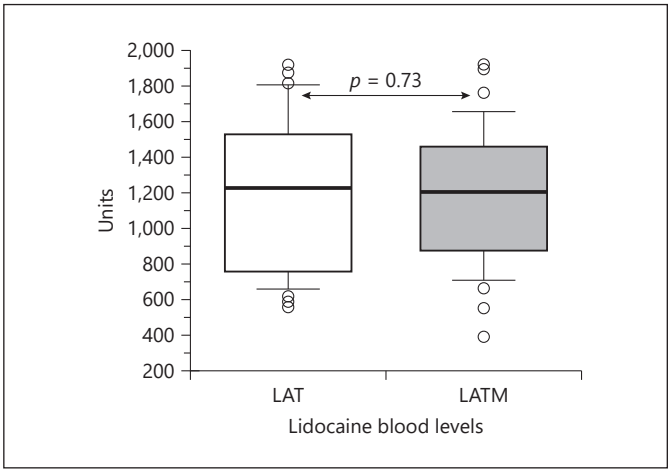

Fig. 2. Lidocaine blood levels according to group. LAT, local anesthetic thoracoscopy; LATM, local anesthetic thoracoscopy with midazolam.

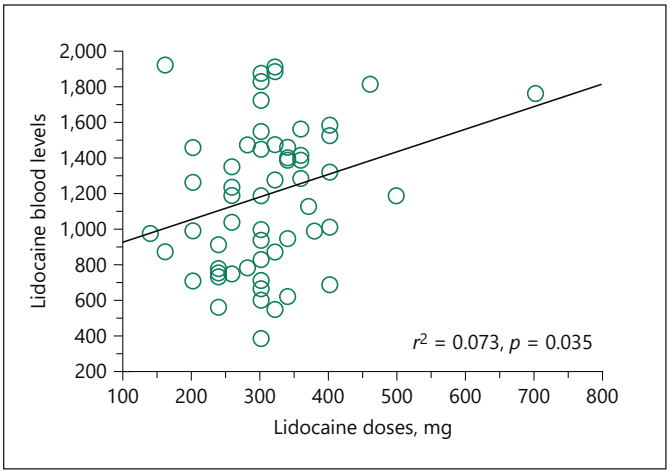

Fig. 3. Regression plot for lidocaine blood levels of all patients according to lidocaine dose administration.

Secondary End Points

Cardiovascular

We experienced a small but significant (p = 0.035) mean drop in heart rate at T15 in the LATM group versus the LAT group, which remained significant (p = 0.025) until the end of the procedure (Tend). Changes in heart rate were not significantly lower between the 2 groups neither at 15 min nor at Tend. Overall, 3 (3.7%) patients presented with bradycardia (<60 rates/min) at any moment of the procedure, all in the LATM group. Only in 1 patient with heart rate (HR) = 45/min we had to administer atropine to palliate his bradycardia. Hypotension (systolic pressure <90 mm Hg) was present overall in 5 patients (6.2%). There were no significant differences in systolic and diastolic blood pressure between the 2 groups at any of the time points (Table 3).

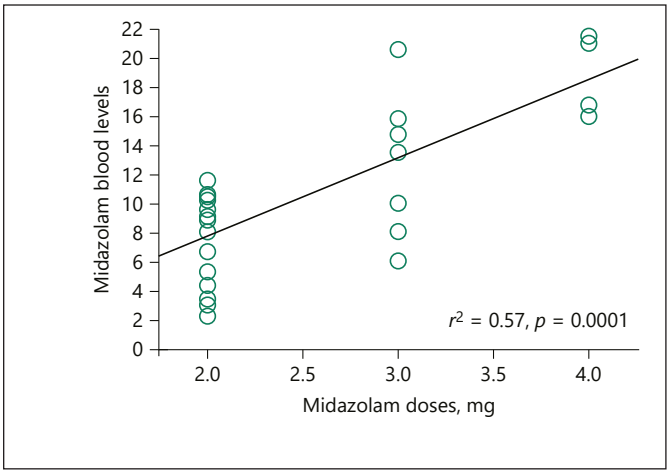

Fig. 4. Regression plot for midazolam blood levels according to midazolam dose intravenous administration.

Other Complications

Twelve (15%) complications (7 for LATM vs. 5 for LAT, p = 0.15) (Table 3) occurred in 9 patients (11.2%). In 1 patient (1.25%), pain led to pethidine IV administration. None of the patients presented with hemorrhage or were transferred to the ICU. No death was recorded in our series.

Procedure Duration, Analgesia, Dosages, and Blood Levels

The duration of the procedure was similar in both groups (Table 3). No significant difference was observed between the 2 groups in terms of days of drainage (p = 0.66) or hospital stay (p = 0.65) (Table 3). Patients received similar (p = 0.38) subcutaneous dose of lidocaine. The mean dose of midazolam was 2.3 ± 0.7 mg (Table 3). Lidocaine blood levels at 30 min were similar (p = 0.73) for both groups: 120.4 ± 42.4 ng/mL for LAT versus 117.1 ± 39 ng/mL for LATM (Fig. 2). Midazolam levels at the same time point for LATM were 105.9 ± 54.1 ng/mL. Overall, there was a statistically significant linear correlation between the subcutaneous administered dose of lidocaine and the lidocaine plasma levels (r^2 = 0.073, p = 0.035) (Fig. 3) and between the IV administered dose of midazolam and its plasma levels (r^2 = 0.57, p = 0.0001) (Fig. 4).

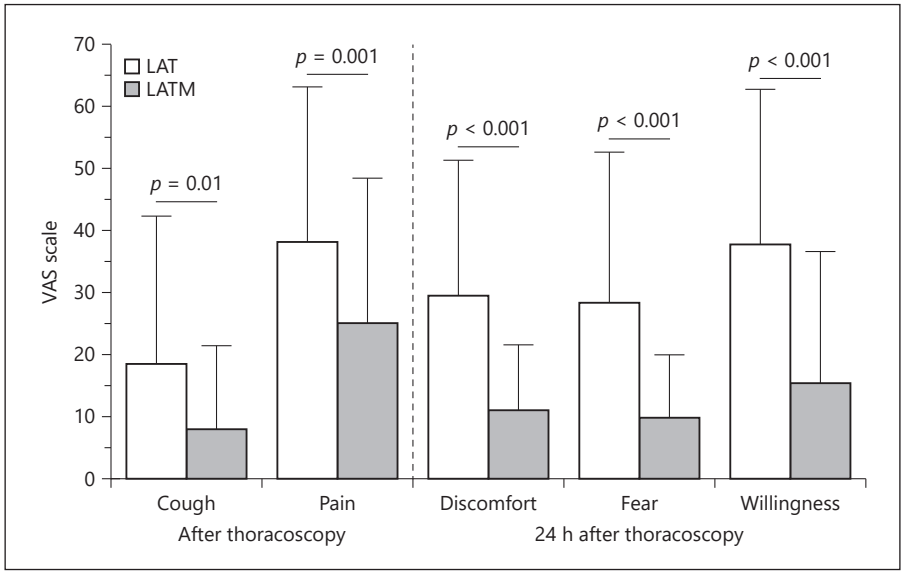

Fig. 5. VAS (0–100 mm) for cough, pain just after thoracoscopy and discomfort, fear, and willingness to repeat the procedure the next day from the LAT versus LATM group. (Scale for cough, pain, discomfort, and fear: 0 = not present and 100 = highly present. Scale for willingness to repeat the procedure: 0 = extremely willing and 100 = not willing at all). LAT, local anesthetic thoracoscopy; LATM, local anesthetic thoracoscopy with midazolam; VAS, visual analog scale.

Quality of Life

Scores for cough, pain, fear, discomfort, and willingness to repeat the procedure are presented in Table 4. After the end of the procedure, the cough ($p = 0.015$) and pain scores ($p = 0.015$) were significantly lower in the LATM. Moreover, 24 h after the procedure, scores for fear, discomfort, and willingness to repeat the procedure were significantly lower in the midazolam group ($p < 0.001$) (Fig. 5).

Table 4. Patients' QoL assessed by VAS (0–100 mm) according to the groups: LAT and LATM

	LAT ($n = 40$)	LATM ($n = 40$)	p value
VAS at the end of thoracoscopy			
Cough	18±23	7±13	0.015
Pain	38±24	24±23	0.015
VAS 24 h after thoracoscopy			
Discomfort	29±22	11±10	<0.001
Fear	28±24	18±23	<0.001
Willingness to repeat	38±24	15±20	<0.001

Data are presented as mean±standard deviation. Scale for cough, pain, discomfort, and fear: 0 = not present and 100 = highly present. Scale for willingess to repeat the procedure: 0 = extremely willing and 100 = not willing at all. LAT, local anesthetic thoracoscopy; LATM, local anesthetic thoracoscopy with midazolam; VAS, visual analog scale; QoL, quality of life.

Discussion

The results from this prospective randomized study support the use of midazolam as a safe and efficient sedative agent in MT. During the procedure, no significant difference in oxygen saturation was observed between the 2 groups. Furthermore, the number of patients presenting a drop in oxygen saturation to below 90% was equal for both groups. Moreover, systolic and diastolic blood pressure did not differ between the 2 groups at any time point, and hypotension was low in both groups of the study. Heart rate was the only hemodynamic parameter that was significantly decreased in the midazolam group at 15 min and at the end of the procedure, but only 1 patient presented with bradycardia that required intervention. Furthermore, we did not observe any severe complications in our study groups, such as major bleeding, respiratory insufficiency, or death.

To our knowledge, this is the first prospective, randomized, non-inferiority trial comparing sedation by midazolam and local anesthesia to local anesthesia only in patients undergoing MT. Our decision to systematically administer midazolam without a combination of an opioid was based on the fact that outcomes should not be influenced by a second drug. Midazolam is used regularly in bronchoscopy [9]. Its use in bronchoscopy is well established due to its rapid onset of action, short half-life, and sedative properties [21]. It has been shown that when midazolam is used alone, it is associated with a lower probability of respiratory suppression and better tolerance than opioids [21, 22]. The association of benzodiaz-

epines with opiates is debated; some authors believe that it is safe [23], while others believe that it results in a greater decrease in oxygen saturation [24]. In a recent review, Astoul and Maldonado [4] stated that data from other procedures should not be extrapolated and that assessing the safety and efficacy of different sedative agents should result from randomized trials. We fully agree with this statement, and as few prospective trials exist in MT, this was one of the reasons we designed the current study. Furthermore, according to our data, the presence of an anesthesiologist might not be mandatory to manipulate such a low dose of midazolam, yet knowledge and experience on this field are mandatory [13].

Few studies exist in MT investigating sedatives. In an observational study, Tschopp and associates [5] optimized the level of sedation individually by titrating the propofol used with opiates in 53 patients. The median dose of propofol was set at 130 mg. Only 4 (7.5%) patients presented hypoxemia during the procedure, and the incidence of cardiovascular complications was 73.5%, all of which were managed in the endoscopy suite [5]. In another Swiss non-inferiority trial, Grendelmeier and associates [6] randomized 90 consecutive patients into 1 group receiving propofol and a second group receiving midazolam prior to MT with the primary end point being the difference in oxygen saturation between the 2 groups. The authors concluded that propofol should not be considered as the first choice for sedation in MT as it leads to a significantly higher incidence of hypoxemia and hypotension than midazolam [6]. These findings are also supported by the interim analysis of Vorster and collaborators' [25] study. The authors randomized 38 patients to either midzolam/fentalyl or propofol/fentanyl administered by a nonspecialized anesthesiologist [25]. They observed significantly more important adverse events and complications ($p = 0.04$) requiring interventions, especially respiratory, in the propofol than in the midazolam group [25]. However, it seems that using a much lower median dose of titrated propofol guided by the level of consciousness, as assessed by the bispectral index (BIS), may prevent these side effects while making the procedure comfortable for the patient [5, 26]. Chhajed et al. [27] investigated hypoventilation during MT in 14 patients; the mean dose of midazolam in their study was 5.7 ± 3 mg, higher than that used in our study. They reported a mean lowest oxygen saturation of 94.9 ± 3.5%, with 1 patient (7%) showing a decrease in SaO_2 below 90% (86%) for 1 min. However, this patient received 50 mg of pethidine, without midazolam, while the dose of hydrocodone he received is unspecified.

At 15 min and at the end of the procedure, the heart rate was significantly lower in the group of midazolam in our study. However, the change from the baseline was similar in both groups. Bradycardia <60 bpm occurred in 3 patients, all in the midazolam group (Table 3), yet only 1 patient necessitated drug administration during the procedure. A significant change from the baseline was noted in the systolic blood pressure at the end of the procedure for LATM compared to LAT. None of the patients necessitated any specific treatment. No significant difference was noted between the 2 groups in the diastolic blood pressure. Classic side effects of midazolam are both bradycardia and hypotension. However, in the study of Grendelmeier et al. [6], hypotension for both systolic and diastolic pressures was more pronounced with propofol than with midazolam. The same findings were noted in the study of Gravino and collaborators [28].

In our study, the overall incidence of complications was low, and the severity was mild (Table 3). There were no severe complications or death due to the procedure in our series. It is well known that MT is a safe procedure where severe complications or death are extremely rare [3]. This is related to the simplicity of the technique, to the experience of the team, and to the selection of patients. Our patients were quite equal in terms of risk for anesthesia, as 45% were ASA I/II and 55% were ASA III/IV. Moreover, the days of drainage and the hospital stay were low, although this concerned patients who were undiagnosed before the procedure, patients with empyema or pleurodesis. Again, our team is experienced, as our data show in terms of duration of the procedure, and combined with the simplicity of the technique, these are probably the most important points to consider.

A first observation regarding the QoL scoring of our groups is that both procedures were very well tolerated. Furthermore, we support the use of midazolam for sedation in patients undergoing MT, as the VAS score at the end of the procedure for both cough and pain was significantly better in the group of patients with LATM. Midazolam has definitely an effect on cough when administered alone for gastroscopy [29] by its central effect on the diaphragm [30], yet the control of pain and cough with opioids seems to be better than with midazolam [21, 22] in endoscopic techniques. However, in the randomized study of Grendelmeir in MT patients, the cough score was equal for both propofol and midazolam as assessed by the physicians and the patients. Moreover, in our study, the day following the procedure, the sensation of discomfort and fear were significantly better in the group of patients with midazolam, as well as the patients'

willingness to repeat the procedure. Again, there is no direct comparison between midazolam and local anesthesia regarding MT in the literature to date. However, when patients were sedated for bronchoscopy with benzodiazepine versus local anesthesia, they tolerated the procedure better [31, 32] and were more likely to agree to repeat the procedure, if necessary [32]. This can be attributed to the amnesic effect of benzodiazepines in the impairment of memory already reported after endoscopic procedures [33, 34, 35]. Midazolam for bronchoscopy in the randomized study of Houghton and associates [22] showed a median VAS score of 3 (2–3) of a maximum of 7, not significant from alfentanil (median 2, range 2–4), which is actually worser than the score in our study.

In our study, both groups that underwent MT had comparable doses of lidocaine for intercostal blockage, in the range that it is indicated not to induce side effects [14]. However, there is no study reporting results on lidocaine dosage in this patient population, and furthermore, to date, no study exists exploring the blood levels of lidocaine so far. In a study dealing with patients undergoing bronchoscopy, Loukides and collaborators [36] have anesthetized their patients with a higher dosage of lidocaine 2% (622 ± 20 mg) than that used in our study. The peak concentration in the serum for lidocaine after 20 and 30 min in their patient population (2.1 ± 0.4 and 1.9 ± 0.3 μg/mL) did not exceed the critical levels of toxicity, and the levels of all patients in their study were significantly related to the administered overall and tracheal doses of lidocaine ($r = 0.63$, $p = 0.05$ and $r = 0.64$, $p = 0.02$, respectively) as we observed in our study. The IV dose of midazolam to achieve sedation in our study was much lower than that in the Gendelmeir study [6] with MT in which patients had 9 mg (6.5–13 mg), but it was comparable to other studies dealing with patients with bronchoscopy. The midazolam peak concentration after bolus IV injection in healthy volunteers is achieved in <3 min and decreases rapidly [17]. There is a linear correlation between plasma concentrations and administered doses [17, 37], like in our study, with the mean biological half-life being 2.2 ± 0.4 h in the Heinzman study [17]. However, the interindividual metabolism of midazolam can differ greatly even in healthy subjects: a comparative study of midazolam bioavailability from 5 different ethnic Chinese groups [38] demonstrated large differences between them. No interference between lidocaine and midazolam exists, as it has been already shown by Shurg and associates [39].

We are mindful of some limitations. The first limitation is the simple size of the study. Like the study of Grendelmeir et al. [6], our study was designed based on hypoxemia as a marker for morbidity instead of peri-interventional mortality. However, MT has an extremely low mortality rate ranging from 0.5 to 1% and relevant complications of up to 3% [1–3]. Thus, the estimated sample size to identify a difference in mortality of 0.5% between the groups would be 15,000 patients, and even for relevant complications, this size would be 1,500 [6]. Another limitation is that we have not assessed the 2 groups for the level of sedation during the procedure as recommended by the ASA [13]. Thus, sedation depth cannot be directly compared between randomized groups. However, as recommended [13], we undertook monitoring by pulse oximetry and blood pressure measurements at defined intervals as well as ECG assessment during the procedure.

Similarly, we have not assessed neuro-psychiatric recovery. Only the study of Tschopp using propofol and opiates [5] assessed recovery after MT, with a time to discharge set at 85 min in most of the cases. In bronchoscopy, Clarkson et al. [34] found in their randomized study of propofol versus midazolam that the patients recovered significantly faster with propofol. These results were later confirmed by Clark and associates [8] who randomized 82 patients undergoing bronchoscopy to receive midazolam or propofol, with the primary end point being the time delay until recovery as assessed by the the time taken to achieve a electroencephalographic BIS above 90 and the secondary end point being the cognitive recovery evaluated by the continuous performance test. The electroencephalographic recovery time (BIS value >90) was significantly shorter ($p = 0.001$) in the propofol group than in the midazolam group (5.4 ± 4.7 vs. 11.7 ± 10.2 min), and the rate of patients with a BIS value >90 at any time after the procedure was significantly higher after propofol than midazolam [8]. The continuous performance test at 15 min after bronchoscopy also showed significant differences for all tested items in favor of the propofol group [8].

A third limitation is that our study was not blinded due to patients' overall management. However, the possibility of assessment bias was counteracted by the careful evaluation of several objective end points, including hemodynamic measurements and outcome parameters [6]. Finally, another limitation is that our study is a single-center study, which always performed the same standardized procedure, which is not the case for studies enrolling patients from many different centers with possible variances in the technique. Therefore, caution might be needed when generalizing these results and introducing this sedation technique to other institutions with less experienced staff.

We conclude that in MT, midazolam when added to lidocaine is a safe choice, with low complications and better

tolerance of the procedure than lidocaine alone. These findings together with the low midazolam dose administered in our study suggest that the presence of an anesthesiologist might not be mandatory during the procedure. In compliance with the results of our study, we already changed the strategy of performing MT in our department.

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Statement of Ethics

The study was approved by the internal review board of the Alexandroupolis University Hospital and Medical School, Democritus University of Thrace (IRB10/10-04-2014), according to Ethics in Good Clinical Practice as addressed by Declaration of Helsinki and Greek Regulations.

Conflict of Interest Statement

The authors state no conflict to disclose. This study was presented as an oral presentation at the Madrid 2019 ERS Congress.

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Author Contributions

Study conception: M. Froudarakis. Protocol design and organization: M. Froudarakis, S. Eleftheriadis, A. Koulelidis, S. Anevlavis, and P. Pappas. Patients' recruitment, inclusion, and management: all authors. Pharmacokinetics: P. Pappas, A. Karkabounas, and V. Boti. Data analysis and interpretation: all authors. Manuscript draft and review: all authors.

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