Rigid Mini-Thoracoscopy Versus Semirigid Thoracoscopy in Undiagnosed Exudative Pleural Effusion

The MINT Randomized Controlled Trial

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Background: **There is debate regarding the ideal instrument for medical thoracoscopy. The authors compared rigid mini-thoracoscopy with semirigid thoracoscopy for thoracoscopic pleural biopsy.**

Methods: **Consecutive subjects with undiagnosed exudative pleural effusion were randomized (1:1 ratio) to mini-thoracoscopy or semirigid thoracoscopy groups. The primary objective was a comparison of the diagnostic yield of pleural biopsy. Key secondary outcomes were the comparison of sedative/analgesic dose, operator-rated and patient-rated pain on visual analog scale (VAS), operator-rated overall procedural satisfaction (VAS), pleural biopsy size, and complications between the groups.**

Results: **Of the 88 screened subjects, 73 were randomized: 36 to mini-thoracoscopy and 37 to semirigid thoracoscopy. Diagnostic yield of pleural biopsy in the mini-thoracoscopy (69.4%) and semirigid thoracoscopy groups (81.1%) was similar on intention-to-treat analysis ($P = 0.25$). Although the operator-rated overall procedure satisfaction scores were similar between groups ($P = 0.87$), operator-rated pain [VAS (mean ± SD), 43.5 ± 16.7 vs. 31.7 ± 15.8; $P < 0.001$] and patient-rated pain (VAS, 41.9 ± 17.3 vs. 32.1 ± 16.5; $P = 0.02$) scores were greater in the mini-thoracoscopy group. Mean dose of fentanyl and midazolam received was similar between the 2 groups ($P = 0.28$ and 0.68, respectively). Biopsy size was larger in the mini-thoracoscopy group (16.1 ± 4.5 vs. 8.3 ± 2.9 mm; $P < 0.001$). Three minor complications occurred in the mini-thoracoscopy group and 6 in the semirigid thoracoscopy group ($P = 0.11$). There were no serious adverse events or procedure-related mortality.**

Conclusion: **Diagnostic yield of rigid mini-thoracoscopy is not superior to semirigid thoracoscopy. Use of semirigid thoracoscope may provide greater patient comfort.**

Key Words: pleural effusion, lung cancer, tuberculosis, thoracoscopy, pleura

(*J Bronchol Intervent Pulmonol* 2020;27:163–171)

Undiagnosed exudative pleural effusion may present as a diagnostic challenge to the respiratory physician. The most common etiologies are malignancy and tuberculosis (TB).[1] It is difficult to differentiate tuberculous and malignant pleural effusions on a clinicoradiologic profile. The diagnostic yield from thoracentesis and/or closed pleural biopsy is suboptimal, leaving ~25% to 40% of these patients undiagnosed.[2,3] Medical thoracoscopy or pleuroscopy is the preferred modality for the evaluation of undiagnosed exudative pleural effusions as it allows pleural visualization and pleural biopsy under direct visualization and has excellent diagnostic yield.[4]

There is debate regarding the ideal instrument for performing thoracoscopy.[5] The most commonly used is the conventional rigid thoracoscope (10-mm external diameter with a 5-mm working channel), though this may be an unfamiliar tool for many pulmonologists.[6] A semirigid/flexi-rigid thoracoscope (Olympus LTF-160; 7.0-mm outer diameter with 2.8-mm working channel) is also available that is similar in design to a flexible videobronchoscope.[7] The utility of a semirigid thoracoscope has been previously reported.[8,9]

Received for publication April 11, 2019; accepted July 29, 2019.
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S.B.: collected data, data analysis, prepared the manuscript. S.M. and P.T.: collected data and manuscript revision. D.J. and S.A.: reported the pathology specimens and revised the manuscript. V.H., A.M., P.M., G.C.K., and R.G.: study design and manuscript revision. R.M.P.: data analysis and manuscript revision. K.M.: conceived the study, study design, manuscript preparation, and revision of the manuscript.

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DOI: 10.1097/LBR.0000000000000620

Two previous RCTs have compared the diagnostic yield of conventional rigid thoracoscope versus the semirigid thoracoscope and found that the diagnostic yield of both the instruments is similar if an adequate pleural biopsy is obtained.[5,10] However, there is a concern that the use of a semirigid thoracoscope may be associated with a greater incidence of inability to obtain an adequate pleural biopsy.[10] The potential advantage of rigid thoracoscope to obtain an adequate pleural biopsy more consistently is offset by greater procedure-related pain and higher requirement of sedation/analgesia with its use. Therefore, each instrument has its advantages and limitations.

Mini-thoracoscope (Richard Wolf GmbH, Germany) is a relatively newer rigid thoracoscopy instrument that has an external diameter smaller (5.5 mm) than the conventional rigid and semirigid thoracoscopes and a working channel (3.5 mm) larger than the semirigid thoracoscope. However, there is scant literature available on its diagnostic yield and no previous study has compared its performance characteristics with the semirigid thoracoscope. We performed a randomized controlled trial (RCT) to compare the diagnostic yield of mini-thoracoscopy with semirigid thoracoscopy in patients presenting with undiagnosed pleural effusion.

METHODS

Study Design

The study was an investigator-initiated, prospective, RCT and subjects were enrolled between July 2016 and June 2018. Institutional Review Board approval was obtained from the Institute Ethics Committee (Ref. No. IECPG-359) and the trial was registered with Clinicaltrials.gov registry (trial identifier: NCT 02851927, www. clinicaltrials. gov). Written and informed consent was obtained from all the participants.

Subjects

Consecutive subjects with undiagnosed exudative pleural effusion were screened for inclusion. Subjects older than 18 years providing consent for participation were included if they were planned for thoracoscopic pleural biopsy for the evaluation of an undiagnosed exudative pleural effusion (defined as a pleural effusion that remained undiagnosed despite diagnostic thoracentesis including negative fluid cytologic examinations and other ancillary investigations). Other essential prerequisites for inclusion were the presence of adequate rib spaces on clinical examination for the successful performance of thoracoscopy and the presence of a pleural effusion amenable for thoracoscopy on a preprocedural thoracic ultrasonography examination. The exclusion criteria were the following: (1) pregnancy, (2) coagulopathy (platelet count $<50{,}000/mm^3$ and/or international normalized ratio >1.5), (3) unstable hemodynamic status (systolic blood pressure >180 mm Hg, diastolic blood pressure >100 mm Hg or systolic blood pressure <90 mm Hg), (4) heart failure, (5) myocardial infarction or unstable angina in the preceding 6 weeks, (6) hypoxemia not correctable with low flow oxygen (SpO_2 <90% despite oxygen at flow rate of 1 to 2 L/min), (7) extensive rib crowding on clinical examination, (8) extensive adhesions and lack of pleural space on thoracic ultrasonography, and (9) refusal of consent.

Randomization

Subjects meeting the inclusion criteria and willing for participation were randomized in a 1:1 ratio into either mini-thoracoscopy or semirigid thoracoscopy groups. The randomization sequence was computer generated and the allocation was concealed in opaque sealed envelopes.

Procedures

Baseline investigations included complete blood count, liver and renal function tests, coagulation profile, an electrocardiogram, and computed tomography scan of the thorax in all subjects. Diagnostic thoracentesis results (including pleural fluid analysis for pH, total and differential cell count, protein, glucose, adenosine deaminase, acid-fast stain, Gram stain and bacterial cultures, and 3 pleural fluid cytology examinations) were available before the enrollment in the study. Pleural effusion was classified as exudative according to Light's criteria. Three operators performed the procedures in both the groups. The use of semirigid thoracoscope was more common at the center before initiation of the study.

For performing procedures in the semirigid thoracoscopy group, the autoclavable semirigid thoracoscope LTF-160 (Olympus Corporation, Tokyo, Japan), was used. For entry port, a 10-mm diameter plastic trocar was used. Flexible forceps (2.8 mm) with alligator jaw and spike was used for pleural biopsy in this group. In the mini-thoracoscopy group, the rigid mini-thoracoscope (Richard Wolf GmbH, Germany) was utilized. It is a 5.5-mm diameter operating metallic laparo-endoscope with a 3.5-mm internal working channel. The direction of view is 0 degrees and a 3.5-mm rigid biopsy forceps with spoon jaws was

used for pleural biopsy. For entry port, a 5.5-mm diameter metallic trocar was used.

Before thoracoscopy, nil per oral status was ensured. The subject was positioned in the lateral decubitus position with the procedure side up. Clinical examination and thoracic ultrasound were performed in all to evaluate the rib spaces, amount of pleural fluid and for selection of the thoracoscope port site. Hemodynamic monitoring included monitoring of vital parameters: blood pressure, pulse rate, respiratory rate, and oxygen saturation. Supplemental oxygen was administered to maintain oxygen saturation $>90\%$ during the procedure. Procedures were performed under moderate conscious sedation using a combination of intravenous benzodiazepine (midazolam) and opioid (fentanyl). The initial doses of midazolam and fentanyl administered were 0.015 mg/kg and 1.5 μg/kg, respectively. Doses were escalated targeting a sedation level where the patient was sedated and verbal contact was possible at all times. A sedation scale was not used. The procedure site was exposed and prepared using chlorhexidine and 10% povidone iodine. The skin, subcutaneous tissue, and parietal pleura were anesthetized using infiltration with 1% lignocaine solution (10 mg/mL), at the incision site. An incision was subsequently made at the preselected site. Blunt dissection was performed and after pleural puncture, trocar was introduced. Preparation steps were similar in both groups. After port creation, the thoracoscope was then inserted through the trocar. Pleural fluid was aspirated and a systematic examination of the pleural surfaces was performed. Minimum of 6 to 8 pleural biopsy samples were obtained with semirigid thoracoscope (owing to the smaller size of biopsies with flexible forceps) and at least 4 with mini-thoracoscopy. Switching to alternative thoracoscope was performed in case of difficulty/inability in obtaining pleural biopsy with 1 instrument. Histopathologic examination, mycobacterial cultures, and Xpert MTB-Rif test were performed on all pleural biopsy specimens. Upon procedure completion, a chest drain was inserted. A chest radiograph was obtained in all subjects following the procedure. Subjects were followed-up to 6 months in case a definite diagnosis was not obtained on pleural biopsy.

Outcomes

The primary outcome was comparison of the diagnostic yield of pleural biopsy in both groups on an intention-to-treat analysis. The biopsy was considered diagnostic if histopathologic findings demonstrated a definite diagnosis of either malignancy or TB or histopathologic findings were consistent with subsequent clinical course and response to treatment on follow-up. If histopathologic examination of pleural biopsy demonstrated normal pleura or nonspecific pleuritis (NSP), then subjects were followed-up for 6 months from the time of procedure for ascertaining the final diagnosis. Secondary outcomes included a comparison of doses of midazolam and fentanyl between groups, operator-rated and patient-rated pain on visual analog scale (VAS), operator-rated overall procedural satisfaction (VAS), pleural biopsy size, and complications between the groups. The VAS for operator-rated and patient-rated pain was anchored between "no pain (0)" and "maximum pain (100)." The VAS for operator-rated overall procedure satisfaction was anchored between "totally unsatisfactory (0 mm)" and "very satisfactory (100 mm)." All subjects were blinded to the instrument used during the procedure.

Statistical Analysis

Considering the yield of semirigid thoracoscopy as 67% [8] and rigid thoracoscopy as 97%,[6] 30 subjects were required in each arm to obtain a power 80% and type 1 error 0.05. Expecting a 20% loss to follow-up, it was planned to recruit 36 subjects in each arm. Data were expressed as mean, SD, median, interquartile range, or as percentages. For continuous variables, comparison between groups was performed using the Student *t* test (or Wilcoxon rank-sum test in case of non-normally distributed data). For categorical variables, comparisons were performed using the χ^2 test (or Fisher exact test). The primary objective was analyzed on an intention-to-treat basis. Treatment received/as-treated analysis was also performed. A *P*-value of <0.05 was considered statistically significant.

RESULTS

Eighty-eight subjects with undiagnosed exudative pleural effusion were screened for inclusion. Fifteen were excluded (6 had minimal effusion on thoracic ultrasound and 9 had extensive rib crowding on clinical examination) and finally, 73 subjects were randomized: 36 to mini-thoracoscopy group and 37 to semirigid thoracoscopy group. Two subjects from mini-thoracoscopy group were crossed over to

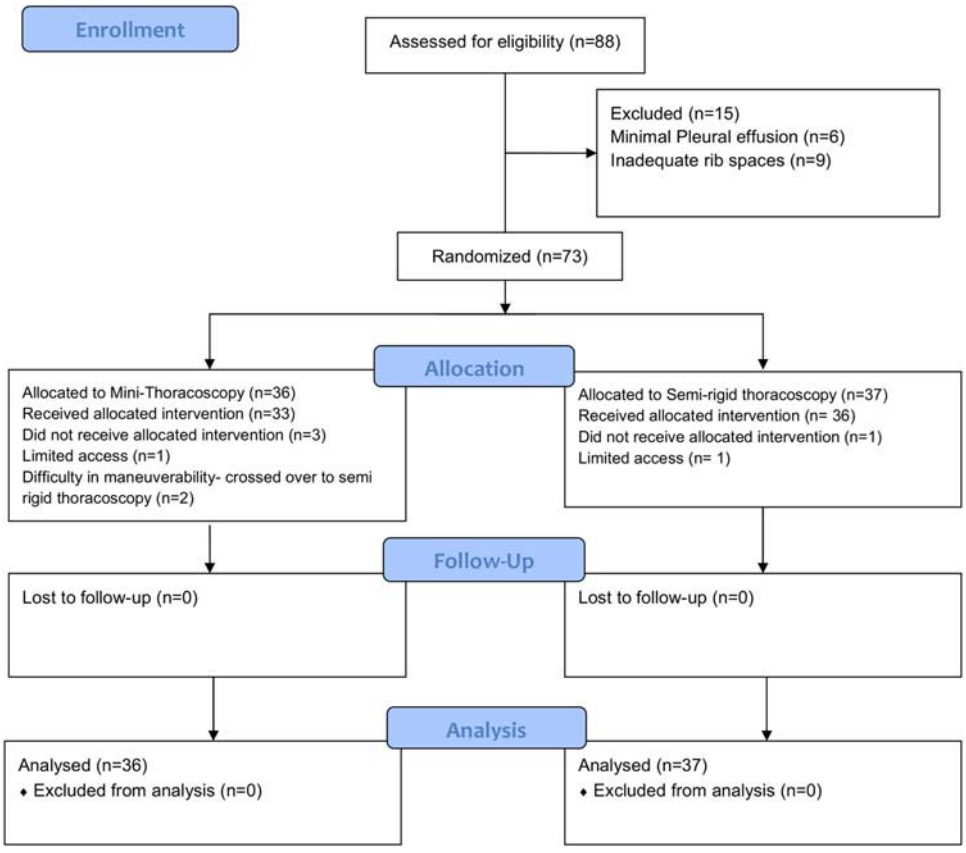

FIGURE 1. CONSORT diagram showing the flow of participants in the MINT randomized clinical trial. MINT indicates MINi-thoracoscopy vs. semirigid Thoracoscopy.

semirigid thoracoscopy because the presence of thick adhesions and difficulty in scope maneuverability with mini-thoracoscope necessitated an attempt with the semirigid thoracoscope. In 2 subjects (one from each group), the procedure was abandoned because of limited pleural access because of dense adhesions. The flow of subjects in the study is shown in the CONSORT diagram (Fig. 1). Baseline clinical characteristics were comparable (Table 1). The mean age of the overall cohort was 50.1 ± 13.9 years. There was no difference between symptoms, duration of symptoms, smoking status, preprocedure clinicoradiologic diagnosis, and comorbidities between the groups. Hypertension and diabetes mellitus were the most common comorbid conditions. Most of the pleural effusions were moderate to large sized. The proportion of patients with the presence of pleural thickening, pleural nodularity, or pleural loculations on thoracic computed tomography scan was similar between the groups. The pleural fluid characteristics were also similar between the groups. The proportion of inconclusive/suspicious cytologic findings for malignancy on pleural fluid examination was similar between the groups.

The proportion of procedures performed by trainee fellows and a specialist consultant was not different between the 2 groups ($P = 0.69$). The procedural dose of lignocaine and the incision size was similar in both the arms. On thoracoscopic visualization, abnormal findings were found in 65 of 73 subjects (89.0%). Normal/shiny pleura was seen in 5 (13.89%) and 3 (8.11%) subjects in the mini-rigid thoracoscopy group and semirigid thoracoscopy group, respectively. The distribution of various findings observed during thoracoscopy has been summarized in Table 2. There was a significant difference between the size of nodules between the 2 groups ($P = 0.03$) and small nodules were present in more subjects in the semirigid thoracoscopy group.

The study outcomes are summarized in Table 3. On intention-to-treat (ITT) analysis, the diagnostic yield of pleural biopsy was 69.4% in mini-rigid thoracoscopy arm and 81.1% in semirigid thoracoscopy arm ($P = 0.25$). Adequate biopsies were obtained in all subjects in both groups.

TABLE 1. Baseline Characteristics of the Study Participants

	Total (N = 73)	Mini-Thoracoscopy (N = 36)	Semirigid Thoracoscopy (N = 37)
Age (mean ± SD) (y)	50.1 ± 13.9	49.9 ± 13.8	50.2 ± 14.1
Sex, n (%)			
Male	31 (42.5)	15 (41.7)	16 (43.2)
Female	42 (57.5)	21 (58.3)	21 (56.8)
Smoking, n (%)			
Active/reformed	11 (15.1)	6 (16.7)	5 (13.5)
Never smoker	62 (84.9)	30 (83.3)	32 (86.5)
Duration of symptoms, median (IQR) (d)	60 (7-240)	60 (10-240)	90 (7-240)
Comorbidities, n (%)	23 (31.1)	12 (33.3)	11 (29.7)
Hypertension	15	7	8
Diabetes mellitus	7	3	4
Chronic kidney disease	5	3	2
Others	7	5	2
Clinical diagnosis, n (%)			
Tuberculosis	23 (31.5)	11 (30.6)	12 (32.4)
Malignancy	47 (64.4)	22 (61.1)	25 (67.6)
Others	3 (4.1)	3 (8.3)	0 (0)
Adhesions on thoracic ultrasound, n (%)	—	15 (41.7)	15 (40.5)
Chest radiograph, n (%)			
Mild effusion	5 (6.8)	3 (8.3)	2 (5.4)
Moderate effusion	35 (47.9)	17 (47.2)	18 (48.6)
Large effusion	19 (26.0)	11 (30.6)	8 (21.6)
Massive effusion	14 (19.2)	5 (13.9)	9 (24.3)
Loculations	14 (19.2)	8 (22.2)	6 (16.2)
Pleural thickening	13 (17.8)	5 (13.9)	8 (21.6)
CT thorax, n (%)			
Pleural thickening	13 (17.8)	5 (13.9)	8 (21.6)
Pleural nodularity	15 (20.5)	9 (25)	6 (16.2)
Loculations	15 (20.5)	8 (22.2)	7 (18.9)
Pleural fluid characteristics			
Protein (mean ± SD) (mg/dL)	4.7 ± 0.9	4.7 ± 0.7	4.8 ± 1.0
Glucose, median (IQR) (g/dL)	100.1 (74.7-112)	91 (74.2-116)	102 (78.5-111)
ADA, median (IQR) (U/L)	23.8 (15-28)	20.5 (16-30.8)	20 (14-24)
Cytology suspicious of malignancy, n (%)	8 (10.9)	6 (16.7)	2 (5.4)

ADA indicates adenosine deaminase; IQR, interquartile range; MINT, MINi-thoracoscopy vs. semirigid Thoracoscopy.

On "as-treated" analysis (analyzing the number of subjects who underwent the actual procedure as per the group analyzed), the diagnostic yield was 75.6% and 84.2% in the mini-thoracoscopy and semirigid thoracoscopy groups, respectively ($P = 0.30$) and was similar between the groups. Overall, a definitive histopathologic diagnosis (either malignancy or TB) was achieved in 48 of 71 subjects (67.6%). Malignancy was found in 37 subjects (52.1%) and TB was diagnosed in 11 subjects (18.2%). NSP was found in 21 (29.6%) and normal pleura were diagnosed in 2 (2.8%) subjects. Adenocarcinoma was the most common primary malignant etiology (28/37) (75.7%). Subjects with nondiagnostic pleural biopsy (n = 23) were followed-up for 6 months. On follow-up, 9 pleural biopsies were found to be diagnostic. Patients who were lost to follow-up/expired pending a final diagnosis or an alternative diagnosis were analyzed as a non-diagnostic pleural biopsy.

The dose of midazolam and fentanyl used was comparable between the 2 groups (Table 3). Biopsy size was significantly larger in the mini-thoracoscopy group (16.1 ± 4.5 mm) as compared with the semirigid group (8.3 ± 2.9 mm) ($P < 0.001$). Operator and patient-rated pain during the procedure (VAS), and operator-rated pain during scope manipulation (VAS) was significantly greater in the mini-thoracoscopy group. The ease of maneuverability was better with semirigid thoracoscope ($P = 0.003$). The ease of taking biopsy, quality of image, and the expectation that the biopsy will yield histologic diagnosis was similar in both the groups. There were no major complications during the study and no procedure-related death. Nine minor complications occurred—3 in mini-thoracoscopy arm and 6

TABLE 2. Procedural Characteristics and Visual Findings on Thoracoscopy

	Mini-Thoracoscopy (N = 36)	Semirigid Thoracoscopy (N = 37)	*P*
Procedural details			
Site of thoracoscope entry, n (%)			
4 Intercostal space	1 (2.8)	1 (2.7)	0.20
5 Intercostal space	18 (50)	26 (70.3)	
6 Intercostal space	17 (47.2)	10 (27.0)	
Axillary line for scope port, n (%)			
Anterior	21 (58.3)	24 (64.9)	0.46
Mid	15 (41.7)	12 (32.4)	
Posterior	0	1 (2.7)	
Proceduralist type, n (%)			
Consultant	12 (33.3)	14 (37.8)	0.69
Fellow	24 (66.7)	23 (62.2)	
Dose of lignocaine (mean ± SD) (mg)	112.9 ± 40.3	116.8 ± 38.1	0.67
Incision size (mean ± SD) (mm)	13.6 ± 4.5	11.9 ± 3.1	0.07
No. biopsies taken (mean ± SD)	7.2 ± 1.7	8.75 ± 2.5	0.76
Duration of procedure (mean ± SD) (min)	29.1 ± 7.9	28.03 ± 9.9	0.63
ICD removal day, median (range)	2 (1-72)	2 (1-62)	0.99
Pleuroscopy examination findings			
Gross visualization pleural findings, n (%)			
Normal/shiny	5 (13.9)	3 (8.1)	0.43
Abnormal	31 (86.1)	34 (91.9)	
Adhesions, n (%)	23 (63.9)	26 (70.3)	0.56
Thin	2/23 (8.7)	8/26 (30.8)	
Thick	2/23 (8.7)	5/26 (19.2)	
Both	19/23 (82.6)	13/26 (50)	
Pleural nodules, n (%)	22 (61.1)	22 (59.5)	0.89
Distribution of nodules, n (%)			
Diffuse	5 (13.9)	6 (16.2)	0.81
Focal	17 (47.2)	16 (43.4)	
Size of nodules, n (%)			
Small	5 (13.9)	15 (40.5)	0.03
Large	0	5 (13.5)	
Both	17 (47.2)	7 (18.9)	
Parietal pleural infiltration, n (%)	26 (72.2)	27 (72.9)	0.94
Diaphragmatic pleural infiltration/nodules, n (%)	15 (41.7)	15 (40.5)	0.92
Visceral pleural infiltration/nodules, n (%)	21 (58.3)	16 (43.2)	0.19
Histopathologic findings on pleural biopsy*			
Malignancy, n (%)	16 (48.5)	21 (55.3)	0.57
Adenocarcinoma	13 (81.25)	21 (100)	
Small cell carcinoma	1 (6.3)	0	
Mesothelioma	1 (6.3)	0	
Metastatic squamous cell	1 (6.3)	0	
Tuberculosis, n (%)	6 (18.2)	5 (13.2)	0.56
Nonspecific pleuritis, n (%)	12 (36.4)	9 (23.7)	0.24
Normal pleura, n (%)	0	2 (5.3)	0.64

*Histopathologic diagnosis is reported for denominator, n = 33 for mini-thoracoscopy and n = 38 for semirigid thoracoscopy, considering the subjects who finally underwent the procedure.

ICD indicates intercostal drain.

in semirigid thoracoscopy arm ($P = 0.11$). Six subjects had subcutaneous emphysema and 2 had postprocedure fever that resolved spontaneously. One subject had procedure site infection that required antibiotic treatment.

DISCUSSION

This RCT failed to demonstrate a superior diagnostic yield of rigid mini-thoracoscopy versus semirigid thoracoscopy for pleural biopsy in the evaluation of undiagnosed pleural effusion and semirigid thoracoscopy was associated with greater patient comfort. We did not observe a greater incidence of inability to obtain an adequate pleural biopsy using the semirigid thoracoscope, therefore, suggesting that both the thoracoscopes can be used for obtaining pleural biopsy in the setting of an undiagnosed effusion.

TABLE 3. Primary and Secondary Outcomes

	Mini-Thoracoscopy (N = 36)	Semirigid Thoracoscopy (N = 37)	Between Group Difference (95% CI)	*P*
Primary outcome				
Diagnostic yield of pleural biopsy (intention-to-treat), n/N (%)	25/36 (69.4)	30/37 (81.1)	11.4 (−9.9 to 30.5)	0.25
Key secondary outcomes				
Diagnostic yield of pleural biopsy (as treated), n/N (%)	25/33 (75.6)	32/38 (84.2)	8.4 (−11.9 to 29.0)	0.30
Diagnostic yield of pleural biopsy (crossovers excluded), n/N (%)	25/34 (73.5)	30/37 (81.1)	7.5 (−13.6 to 28.5)	0.46
Dose of midazolam (mean ± SD) (mg)	1.8 ± 0.8	1.8 ± 0.7	—	0.68
Dose of fentanyl (mean ± SD) (μg)	79.3 ± 25.4	73.1 ± 23.1	—	0.28
Biopsy sample size (mean ± SD) (mm)	16.1 ± 4.5	8.3 ± 2.9	—	**0.0001**
Operator-rated overall procedure satisfaction, VAS (mean ± SD) (mm)	84.5 ± 13.1	84.9 ± 7.4	—	0.87
Operator-rated pain, VAS (mean ± SD) (mm)	43.5 ± 16.7	31.7 ± 15.8	—	**0.0001**
Patient-rated pain, VAS (mean ± SD) (mm)	41.9 ± 17.3	32.1 ± 16.5	—	**0.02**
Procedure-related complications, n (%)	3 (9.1)	6 (15.8)	—	0.10
Subcutaneous emphysema	2	4	—	
Fever	1	1	—	
Incision site infection	0	1	—	
Other outcomes				
Adequacy of pleural biopsy, n (%)	33/33 (100)	38/38 (100)	—	
Quality of image, VAS (mean ± SD) (mm)*	68.5 ± 20.1	71.5 ± 17.2	—	0.50
Difficulty of scope maneuverability, VAS (mean ± SD) (mm)†	54.2 ± 23.3	39 ± 21.9	—	**0.003**
Operator-rated pain during scope manipulation, VAS (mean ± SD) (mm)‡	43.1 ± 19.6	33.3 ± 18.1	—	**0.03**
Ease of taking biopsy, VAS (mean ± SD) (mm)	44.6 ± 25.0	50.1 ± 22.5	—	0.33
Expectation that biopsy will reveal histologic diagnosis, VAS (mean ± SD) (mm)§	83.9 ± 16.7	82.2 ± 14.9	—	0.64

Bold values indicate statistically significant ($P < 0.05$).
*Quality of image (VAS)—anchored between worst (0) and excellent (100).
†Difficulty of scope maneuverability and ease of taking a biopsy (VAS)—anchored between very easy (0) and most difficult (100).
‡Operator-rated pain during scope manipulation (VAS)—anchored between no pain (0) and maximum pain (100).
§Expectation that biopsy will reveal histologic diagnosis (VAS)—anchored between least likely (0) and highly likely (100).
CI indicates confidence interval; VAS, visual analog scale.

Our study has many limitations. It was a single-center study; sample size is small and the anticipated difference in the diagnostic yield was not observed. The study was powered as a superiority study although a noninferiority study (requiring a large number of subjects) would be the ideal way to perform such a study. The findings of our study can be taken as preliminary findings that need to be confirmed in adequately powered future studies. The prevalence of scirrhous pleura and malignant mesothelioma was low in our study setting. In our study, 1 subject was diagnosed with malignant mesothelioma in the mini-thoracoscopy arm. In subjects with suspected mesothelioma, multiple, deep and large biopsies (preferably including fat and/or muscle to assess tumor invasion) may be needed for getting adequate biopsy samples.[11] This may be especially important in a sarcomatoid variant of mesothelioma. Therefore, the results may not be generalizable to populations or settings with a higher incidence of malignant mesothelioma. In such situations, there may be a difference in the yield of 2 instruments and a larger RCT may bring more clarity in this regard. The findings of the study may not be generalizable to settings where the procedures are performed under deep sedation or general anesthesia as the procedure discomfort issues with 1 instrument may be less apparent in that situation. The procedure was

performed by different operators that may lead to subjective variation in the VAS assessment. However, this is unlikely to be significant as the proportion of procedures performed by a fellow or consultant were similar between the groups. No conclusion can be drawn regarding the comparative characteristics of the 2 instruments for advanced thoracoscopy procedures like adhesiolysis as this was not the primary aim of this study.[12] Although successful performance of adhesiolysis has been reported with a semirigid thoracoscope, the rigid thoracoscope is an intuitive choice in this regard.

Malignancy was the most common etiology in our study and the most common histopathologic diagnosis was adenocarcinoma lung that was consistent with the previous studies.[13,14] The incidence of TB was lower (18% vs. 25%) than the other studies from similar settings.[10] This is likely a referral bias as ours is a tertiary care referral institute. Subjects with clinically suspected tubercular pleural effusion are often started on empirical ATT, may improve subsequently and are less likely to present to a tertiary care facility.

An observation in our study was the need for conversion of procedure from rigid to the semirigid instrument in 2 subjects. This was required because of presence of thick adhesions wherein excessive manipulation with the rigid instrument was considered risky. The procedure could be performed successfully after conversion to a semirigid thoracoscope and the observed advantage included better image and angulation capability because of flexibility at the tip. This is contrary to the observation in a previous RCT wherein 7 procedures were converted from semirigid to rigid thoracoscopy because of dense adhesions.[10] The angulation capability of the semirigid thoracoscope is especially important as it also prevents injury to the ribs and decreases procedure-related pain. Pain during scope manipulation was also significantly lower in the semirigid group. The overall maneuverability as assessed by VAS score was also easier with the semirigid thoracoscope. However, the possibility of bias cannot be excluded entirely in the interpretation of these observed benefits with the semirigid thoracoscope as the operators were not blinded for pain and procedure satisfaction assessments. Incision size was also observed to be larger in the mini-thoracoscopy group (though statistically nonsignificant). Despite biopsy size being smaller, semirigid thoracoscopy was able to provide diagnostic yield in most of the patients. This agrees with the previous studies.[5,8–10] The choice of instrument may eventually depend upon the operator and the prevalence characteristics of mesothelioma in the population. In case of the high prevalence of mesothelioma in the population, rigid thoracoscopy may be preferred owing to its ability to take deeper pleural biopsies. Operator experience is important regardless of the instrument used to ensure the correct sites for obtaining pleural biopsy while performing thoracoscopy. The overall yield of thoracoscopy was lower in our study than the previous RCTs.[5,10] A greater number of subjects who had NSP were considered as diagnostic pleural biopsy in a previous study and loss to follow-up or any mortality during the study were not reported.[10] These are possible reasons for a lower overall diagnostic yield of thoracoscopy in our study. The observed difference in the lower biopsy yield in our study as compared with other studies may be attributed to smaller sample size. In our study, subjects who expired without a diagnosis or lost to follow-up or subjects who improved on empirical treatment were considered nondiagnostic.

This is the first RCT comparing the mini-thoracoscope with the semirigid thoracoscope for pleural biopsy in undiagnosed pleural effusions. The strength of the study was the rigorous follow-up. Second, an aggressive effort was made to establish the diagnosis in subjects with NSP. We did not find a superiority of rigid mini-thoracoscopy over semirigid thoracoscopy for performing a thoracoscopic pleural biopsy in undiagnosed exudative pleural effusions.

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