Original Article

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TANAFFOS

The Use of Flexible Bronchoscope for Diagnostic Medical Thoracoscopy in a Resource-Limited Setting: A Retrospective Study

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Background: Exudative pleural effusion (ePE) is a common presentation in pulmonology clinics. Pleural biopsy is indicated for identifying the etiology in undiagnosed ePE, especially those with low adenosine-deaminase levels. Access to rigid and semi-rigid medical thoracoscopy is scarce and heterogeneous in a resource-limited country like India. In such circumstances, using a flexible bronchoscope via an intercostal chest tube for visualization of the parietal pleura and pleural biopsy offers a way out.

Materials and Methods: In this retrospective study, we have presented our experience of such practice on 25 cases. Mean age was 52.4±1 years. Adhesions were present in 40% of the subjects.

Results: The most common finding was the presence of nodules. On average, 6.8 passes were taken with a maximum of 10. In 32% cases, only tiny tissue was obtained, hence requiring multiple passes. Large tissue could be obtained in 44% of the subjects. The mean duration of the procedure was 35.6±9.0 minutes. Tissue diagnosis was established in 80% with the most common being malignancy (48%), followed by tuberculosis (20%). In 3 cases, the final diagnosis was made by exclusion. No major complications were recorded.

Conclusions: In conclusion, medical thoracoscopy using a flexible video bronchoscope via intercostal chest tube was a feasible alternative for the diagnosis of ePE effusion in resource-limited settings.

Keywords: Bronchoscope; Medical Thoracoscopy; Tuberculosis; Pleural Effusion; Malignant Pleural Effusion

INTRODUCTION

Pleural effusion, a common disorder in pulmonary medicine, results from a diverse range of causes, including localized pleural or lung diseases, systemic diseases, and drug treatments. Generally, pleural effusions related to localized causes are exudative, whereas systemic causes lead to transudative effusions. Swift identification of the underlying etiology and initiation of early treatment are key factors in determining morbidity and mortality in patients with pleural effusions. In India, the two most common causes of exudative pleural effusion are tuberculosis and malignant pleural effusion (1). The commonly employed algorithm for the diagnosis of pleural effusion is to do a diagnostic pleural tap. The bare minimum investigation includes total count with differentials, protein & sugar, LDH, ADA (adenosine deaminase), and cytological assessment (2). However, despite employing appropriate investigations, delineating

the etiology remains a challenge in 20-25% of pleural fluid patients (3). In such instances, pleural biopsy is considered the gold standard investigative method for establishing a diagnosis. Historically, a blind percutaneous biopsy of the parietal pleura was conducted, which has now been largely supplanted by imaging (USG/CT) guided biopsies or biopsies through diagnostic medical thoracoscopy (4).

In 1910, Swedish internist Hans Christian Jacobaeus introduced the concept of thoracoscopy for pulmonary tuberculosis patients to achieve lung expansion via lysis of pleural adhesions (5). Over the last century, thoracoscopy has seen remarkable progress in the form of being done under general anesthesia to a day care procedure in the current era. This minimally invasive outpatient procedure, done under conscious sedation and local anesthesia, is generally performed by a pulmonologist, enables exploration of both parietal and visceral pleural surfaces. Furthermore, it allows for biopsy samples to be obtained from the affected site under direct visualization, accounting for its higher diagnostic yield compared to percutaneous/closed or blind pleural biopsy (6).

While historically thoracoscopy was performed using a rigid thoracoscope, the evolution in (diagnostic) medical thoracoscopy led to the advent of semi-rigid thoracoscopes. These devices offer added advantages such as easy maneuverability, smaller incision sites, reduced anesthetic requirements, and decreased post-operative pain/discomfort. Despite the invention of medical thoracoscopy a decade ago, its accessibility and implementation remain limited in developing nations such as India. This is primarily due to the cost, unavailability of equipment (thoracoscopes) in several tertiary care facilities, and a lack of trained physicians (7).

In such circumstances, to obtain a pleural biopsy under vision, we developed an unconventional technique to perform diagnostic medical thoracoscopy. The department has a functional bronchoscopy suite where flexible video bronchoscopies are routinely conducted, but the equipment for either rigid or semi-rigid bronchoscopy was not available. The study site is a tertiary care hospital where patients in need of a pleural biopsy are commonly referred. Closed/blinded or ultrasound-guided pleural biopsies were routinely performed; however, the yield remained poor. In order to conduct pleural biopsies under vision, a new makeshift arrangement was made with the use of an intercostal chest tube and flexible bronchoscope.

We performed 25 such procedures over a period of approximately one and a half years on consenting eligible subjects, following which the department got its first semi-rigid thoracoscope. Here we are reporting our experience with this novel practice.

MATERIALS AND METHODS

We conducted a retrospective study in the Department of Pulmonary and Critical Care Medicine at a tertiary care university teaching hospital in Northern India. Medical records of all subjects who had undergone diagnostic medical thoracoscopy using a flexible video bronchoscope from January 2018 to August 2019 were retrieved and analyzed. Being a retrospective analysis, permission to access the records was sought from the head of the institute (medical superintendent), and consent was waived off by the biomedical research and ethics committee vide letter number BREC/22/2603 dated 15 December 2022.

Data of all adult patients aged 18 years and above, who had undiagnosed exudative pleural effusion and underwent medical thoracoscopy via a flexible video bronchoscope inserted via an intercostal chest tube, were retrieved and recorded. Before the thoracoscopy, each patient underwent a chest ultrasound to identify any pleural adhesion or thickening, and a flexible bronchoscopy was performed to identify any intrabronchial growth or obstruction as per the standard protocol. Subjects having extensive adhesions, trapped lung due to pleural thickening, were excluded from medical thoracoscopy.

To describe the technique in brief, after obtaining informed consent for the procedure, patients were positioned in the lateral decubitus position. A chest

ultrasound was performed to identify the site with maximum pleural fluid thickness, and the skin was sterilized using chlorhexidine. Further after sterilization with povidone iodine, local anesthesia was administered with 2% lidocaine at and around the marked point. Subsequently, a 32 Fr chest tube was inserted through an approximately 1.5 cm chest incision (and blunt dissection). Patients were then sedated with initial boluses of midazolam and fentanyl. A flexible video bronchoscope (Olympus BF-1T180 bronchoscope with CV-180 video processor and CLV-180 light source) was introduced into the pleural space through the intercostal chest tube (ICT) (Figure 1).

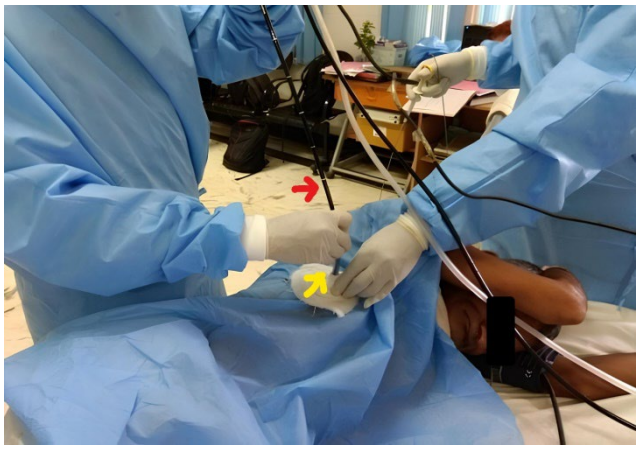

Figure 1. Representative image of the procedure showing the flexible bronchoscope (red arrow) transversing through the intercostal chest tube (yellow arrow), which is acting as a port.

After insertion and visualization of the pleural cavity, the parietal pleura was inspected. Careful handling of the bronchoscope was required to avoid excessive bending of the scope outside of the thoracic cavity. Another difficulty encountered during the procedure was holding the scope near the thoracic cavity, as it was covered by the ICT. Still, the navigation of the scope inside the pleural cavity was largely smooth, and most of the pleural surfaces could be examined with ease. Following inspection of the parietal pleura, biopsy samples were obtained using Olympus reusable endojaw biopsy forceps FB-20C-1/202C-1. The site of sampling was selected based on the findings of observation. Most biopsies were taken from abnormal-looking pleura or nodules, but in a few cases with normal pleura, random biopsies were also taken. Throughout the procedure, blood pressure, pulse rate, electrocardiogram, and continuous pulse-oximetry were closely monitored. Intermittent boluses of midazolam or fentanyl were also given for conscious sedation at the discretion of the operator. After completion of the procedure, the same chest tube was secured in the pleural cavity through the same port and was attached to a water seal (in a drainage bag). Following the procedure, selective cases required parental analgesics in the form of diclofenac or tramadol injections. ICT was kept in situ till the output decreased to less than 100 ml per day. In the case of malignant pleural effusion, pleurodesis was subsequently done using povidone iodine. No antibiotics were administered either during or after thoracoscopy unless indicated, and all manipulations were performed aseptically.

The diagnostic yield and complications were evaluated. We were unable to assess the pain and discomfort outcomes as they were not routinely documented in the procedure notes. Clinical, demographic, pleural fluid characteristics, radiological findings, hospital stay, and thoracoscopic findings were recorded. As we were comparing a modification of the diagnostic technique, we specifically focused on the diagnostic yield of the procedure. Diagnostic yield was measured in terms of final tissue diagnosis with adequacy of the tissue for molecular analysis (in case of non-squamous non-small cell lung cancer) and the size of the tissue obtained with the biopsy forceps. As the data regarding operator ease is not routinely recorded, we used the duration of the procedure as a crude representative. Hospital stay and development of empyema were also analyzed to assess the safety of the procedure.

Data was collected in paper format initially and later entered into a Microsoft Office® Excel sheet. After coding in the Excel sheet, the data was transferred for analysis in SPSS version 26.0 by IBM®. Data was presented descriptively as means (and standard deviation) or

numbers (percentage with 95% confidence intervals) or medians, depending upon the type of variables. We compared the baseline characteristics and other findings among various groups stratified according to either sex, diagnosis, diagnostic yield, or size of tissue obtained. The size of tissue obtained is routinely recorded in the following manner: tissue smaller than the cup of the forceps is tiny, just filling the cup is moderate, and tissue bigger than the size of the cup is labelled as large. Categorical data was compared between the two groups using the Pearson Chi-square test, whereas the difference between continuous variables was analyzed using an independent Student's t-test. For all outcomes, a two-sided p-value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Over a period of 18 months, 28 thoracoscopies via flexible bronchoscopes were conducted in the interventional pulmonology suite of the institute, data of 25 of which have been presented here (Figure 2).

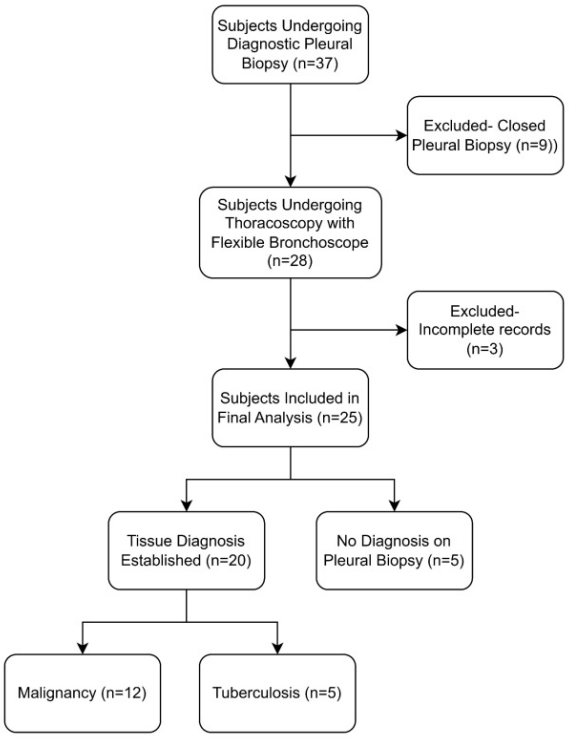

Figure 2. Flow diagram showing the case selection for the study analysis

Most of the subjects were males (56%) and belonged to a rural background (64%). Mean age was 52.4±14 years. The majority of the females were housewives (81.8%), and most of the males were farmers (57.1%). 48% subjects had fever at the time of presentation, followed by cough and dyspnea (both 28%). Constitutional symptoms were present in the majority of cases (loss of appetite in 58% and loss of weight in 40%). Radiological evaluation revealed that the left side was most commonly involved (60%), but the lung parenchyma was normal in 48%. Lung mass was reported in 16% whereas nodules were present in 24% cases. Mediastinal lymphadenopathy was reported in 36%. 16% had mild effusion (defined as occupying less than one-third of the hemithorax). Three subjects had a chest tube in situ at the time of the procedure. Pleural fluid analysis data showed that 56% had straw colored and only one had chylous effusion based on appearance. Atypical cells were reported in 24% of the cytology, but none of them had a conclusive diagnosis on cell block analysis. Mean total cell count was 418±288.3 per µl. 84% had mononuclear cell-predominant differential count. All pleural fluid samples were exudative, and the mean LDH was 375.2±266.7 IU/l, whereas the mean pleural fluid proteins were 5.1±1.2 gm/dl. High ADA (greater than 70IU/l) was reported in only two cases, while both had lung mass in the CECT thorax. Mean ADA in the study population was 29.1±18.6IU/l. Baseline characteristics are provided in Table 1.

During medical thoracoscopy, all surfaces of the pleura were inspected. Adhesions were present in 40% of the subjects. The most common finding was the presence of nodules. 40% of the subjects had crops of fine nodules present, whereas 60% of the subjects had discrete nodules of variable sizes. Five subjects had normal shiny pleura at all surfaces. On average, 6.8 passes were taken with a maximum of 10. In 32% cases, only tiny tissue was obtained, hence requiring multiple passes. Large tissue could be obtained in 44% of the subjects. Mean duration of the procedure was 35.6±9.0 minutes, requiring dual sedation with midazolam (mean 3.7±1.3 mg) and fentanyl (mean 108.0±24.7 µg).

Table 1. Baseline characteristics of the study population. SD: Standard Deviation; LAP: Lymphadenopathy; LDH: Lactate Dehydrogenase; ADA: Adenosine Deaminase

Variable		n(%)
Age in years (Mean±SD), Range		52.4±14.0, 22 to 74
Sex	Male	14(56)
	Females	11(44)
Residence	Urban	9(36)
	Rural	16(64)
Occupation	Farmer	8(32)
	Homemaker	9(36)
	Skilled Job	4(16)
	Desk Job	4(16)
Duration of symptoms in days (Mean±SD)		24.7±18.0
Symptoms	Fever	12(48)
	Cough	7(28)
	Dyspnea	8(32)
	Constitutional Symptoms*	24(96)
Radiological Features	Normal	12(48)
	Lung Nodules	6(24)
	Mass	4(16)
	Consolidation	3(12)
	Mediastinal LAP	9(36)
Pleural Fluid work up	Appearance (Straw, Haemorrhagic, Chylous)	14(56), 10(40), 1(4)
	Total Cell (mean±SD)	418±288.3
	Protein in gm/dl (mean±SD)	5.1±1.2
	Sugar in mg/dl (mean±SD)	70.6±36.3
	LDH in IU/L (mean±SD)	375.2±266.7
	ADA in U/L (mean±SD)	29.1±18.6

None of the patients complained of any severe pain or met with any major complications. Tissue diagnosis was established in 80% with the most common being malignancy (48%), followed by tuberculosis (20%). All subjects of malignancy had sufficient tissue for immunohistochemistry. Nine subjects had lung as a primary tumor (all adenocarcinoma). In 3 cases, the final diagnosis was made by exclusion, one in each- uremic pleuritis, effusion secondary to pulmonary embolism, and congestive heart failure. Hospital stay was prolonged in 3 subjects who had developed empyema after the procedure. All these subjects had insertion of a chest tube in the emergency department, where they had presented with dyspnea at rest and massive pleural effusion. The overall average hospital stay was 3.44±2 days.

Subsequently, we compared the characteristics of the subjects grouped according to the diagnostic tissue yield of the procedure. Using the chi-square test, it was found that Loss of appetite was more common in patients without a definite tissue diagnosis (p=0.032), and subjects with a crop of nodules were at higher risk of not getting a conclusive tissue diagnosis (p=0.02). Also, as anticipated, tiny tissue samples were associated with a high probability of not getting a tissue diagnosis (p=0.006). None of the other variables were significantly different between the two groups. Using the independent sample t-test, we also compared the means of the continuous variables among the two groups, but none of them were found to be significantly different except age, which was higher in the subject without a diagnosis (61.8 versus 48 years, p=0.01). Finally, we tried to analyze the factors associated with the size of tissue. Both the moderate and large tissues were clubbed together as sufficient samples. Only the diagnosis of tuberculosis was found to be an independent risk factor of getting tiny tissue samples (p=0.01), and none of the other variables were found to be significantly different between the two groups.

DISCUSSION

In the current retrospective study assessing the feasibility of doing diagnostic medical thoracoscopy using a flexible video bronchoscope through an intercostal chest tube, including 25 subjects, we found that the diagnostic yield was 80% with large-sized tissue biopsy in 44%. None of the patients had any significant complications during the procedure, and 3 (12%) patients developed empyema.

Medical thoracoscopy is a vital modality for any interventional pulmonology suite, but the availability of equipment in India is grossly heterogeneous (geographically) and limited to major cities only. Whereas the need for such a diagnostic procedure is very high. Pleural effusion is one of the common presenting manifestations of tuberculosis as well as malignancy.

Extrapulmonary tuberculosis (EPTB) comprises nearly 40% of all TB cases, and pleural TB is the most common type of EPTB (8). The majority of such cases are diagnosed on the basis of ADA levels in pleural fluid, as the microbiological evidence in the form of CBNAAT (cartridge-based nucleic acid amplification test) or AFB stain/culture has low sensitivity (9). Despite the sensitivity of ADA levels, a significant proportion of pleural tuberculosis cases are left without diagnosis and in need of diagnostic pleural biopsy (10).

Malignant pleural effusion, similarly, represents a common problem in clinics. Exudative pleural effusion with low ADA with or without hemorrhagic pleural effusion is frequently attributed to an underlying malignancy. Pleural fluid cytology and cell block assessment can help in identifying the underlying cause, but sensitivity remains low (11). In such scenarios, pleural biopsy offers an additional advantage for the diagnosis as well as molecular profiling of the tumors using methods like Next Generation Sequencing and Fluorescent in Situ Hybridization. Following the recent revolution in the management of non-small cell lung cancer (which is the most common cause of malignant pleural effusion), tissue has become a vital source of information, affecting management at all levels. The list of recommended molecular tests (to be conducted on tissue samples) after histology and immunohistochemistry is growing day by day. As per NCCN recommendations, EGFR (done by RT-PCR), ALK (done by IHC), and ROS1 (done by FISH) are the bare minimum investigations that require adequate quantities of tissue samples (12).

Thoracoscopy-guided pleural biopsy offers the exact same advantage over cytology and cell block. A big chunk of tissue samples provides an opportunity to comprehensively investigate for targetable genetic alterations in one single attempt. This makes malignant pleural effusion an important indication for diagnostic medical thoracoscopy.

In addition to this, the availability of the equipment and the expertise is grossly limited in India. In a recent survey by Madan et al., nearly half of the respondents (physicians performing medical thoracoscopies routinely) had an experience of 3 years or less. Though the survey did not include place of practice, nearly half of the participants were from multi-specialty hospitals, with the majority using standard equipment. Commonly, such facilities are limited to tier 1 cities in India (13). Using a flexible bronchoscope for the visualization of parietal pleural and pleural biopsy is not a novel technique and has been tested previously in anecdotal reports, more so by the surgeons (14, 15). In a Japanese study, the technique of using an intercostal chest tube as a trocar/port and bronchoscope for pleuroscopy was tested on seven cases, and it was found to be safely tolerated (16).

Similar to our results, we found that thoracoscopy with a flexible bronchoscope was well tolerated and had no major complications. Additionally, looking at the efficacy of such a technique in the diagnosis, it was revealed that the final diagnosis could be established in 92% (23/25) of the subjects, which was similar to previous studies on semi-rigid thoracoscope (17, 18). When compared to the results of the MINT trial, the tissue diagnostic yield in our study was 80% compared to 81.1% in the semi-rigid arm of the trial (19). The MINT trial also compared the size of the tissue obtained, and the size was measured in millimeters. This is not a routine practice in our institute, and we assess the tissue size based on the gross visualization and comparing with the cup of the forceps.

Another important observation in our study was that the duration of the procedure was less than that compared with the study conducted by Dhooria et al. (53.4±10.8 minutes in semirigid arm versus 35.6±9.0 minutes in our study) (20). This could have been due to the choice of countdown time. We started timing the procedure once the chest tube had been inserted. It is also reflected from the results of the MINT trial, where the duration of the procedure was similar to our study in the semi-rigid arm (28.03 ± 9.9 minutes) (19). Assessing the safety of the procedure concerning the development of empyema, the results of our study were similar to the previous studies

(21). However, as all these cases had an intercostal chest tube in situ before the procedure was planned (in the emergency department), the development of empyema might not have been related to the procedure. We did not face any case of significant subcutaneous emphysema in our study, which is one of the commonly reported complications of the pleuroscopy procedure (12.5%) using a semirigid scope (22). This could have been probably due to the retrospective nature of the study, and mild subcutaneous emphysema is not recorded in hospital records.

Procedure-related pain is one of the factors that gives semi-rigid thoracoscopy an advantage over rigid one and hence has been an important secondary end point in such clinical studies. Procedure-related pain has been commonly measured using visual analogue scales, but as ours was a retrospective study and VAS was not routinely employed, we had to use other surrogate variables. One of such variables was the use of a sedative/analgesic agent during the procedure, which is routinely recorded and can be found in hospital records. However, the previously published literature has widely different reported values for these agents (1.8±0.7 for midazolam in the MINT trial versus 3.9±1.3 mg for midazolam by Dhooria et al.) (19, 20). This suggests that pain management has largely been dependent upon the operator's perceptions and preferences. In support of our results, the values of fentanyl and midazolam used in our studies have been similar to what was reported from a study by Tousheed et al., which is one of the largest data sets in the world in the field of medical thoracoscopy (23).

Another important variable that needs to be analyzed while assessing a new technique for an established procedure is the physician's comfort. There was no way for us to analyze this factor retrospectively. The use of a bronchoscope in place of a thoracoscope has several limitations as far as operator comfort is concerned. The greater length of the scope hinders the maneuverability and limits the ease of approach. Additionally, the inability to pincer holds the scope near the chest wall due to the intercostal chest tube is an additional factor working against the practical utility of the new technique. The proposal of using a standard trocar in place of a chest tube for insertion of a bronchoscope was considered in the initial stage, but due to the flexible and delicate nature of the scope, and its length, it was very likely that the scope may get damaged due to the hard ring of the trocar. Hence, the chest tube was selected as the port of entry. Another difficulty faced by the operator during the procedure was the frequent need to manipulate the depth of insertion of the chest tube so as to provide space to the distal tip of the bronchoscope to make movements inside the cavity.

Our study offers the largest experience of using a bronchoscope for pleuroscopy and confirms its applicability in terms of efficacy as well as safety; however, there are several limitations to our findings. A retrospective study limits our findings to only those variables that are recorded. Also, the experience is collected from only one center, and center-specific practices may influence the outcomes. One such practice is the routine admission of thoracoscopy subjects, which is not commonly done in other centers. We admit all cases of thoracoscopy till the chest tube is out to reduce the risk of complications. Other limitations have been our inability to record pain and operator ease outcomes, which are otherwise important factors while choosing the modality of access. Comparison of our findings with semi-rigid thoracoscopy (now available at our center) would have added value to our findings, but a case-control study increases the risk of selection bias, and hence, we planned to limit our results to a descriptive study.

CONCLUSION

In conclusion, we found that, when needed, the innovative use of a flexible bronchoscope through a chest tube for performing medical diagnostic thoracoscopy is feasible, safe, and probably as successful in obtaining tissue as semi-rigid thoracoscopy. Such a technique can help navigate the limitations of the availability of equipment in resource-limited conditions. However, the

real impact on patient comfort and operator ease needs to be evaluated in larger head-to-head comparative studies.

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Disclosure/Conflict of interest

None to declare

Data Sharing Statement

The anonymized individual patient data can be shared upon request to the corresponding author. All authors have contributed substantially to the current research work, drafting the manuscript, final approval, and are accountable for all aspects of this study.

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