Comparison of the diagnostic yield of transbronchial lung biopsies by forceps and cryoprobe in diffuse parenchymal lung disease

M S Khot,[1] MBBS, DNB (Respiratory Medicine); **A Chakraborti,**[1] MBBS, DTCD, DNB (Respiratory Medicine); **J K Saini,**[1] MBBS, MD; **P Sethi,**[1] MBBS, MD; **S Mullick,**[2] MBBS, MD; **R Saxena,**[3] MBBS, MS; **A R Wani,**[1] MBBS, DNB (Respiratory Medicine)

[1] *Department of Pulmonary Medicine, National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India*
[2] *Department of Pathology, National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India*
[3] *Department of Thoracic Surgery, National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India*

Corresponding author: *J K Saini (jitendralrs123@gmail.com)*

Background. Transbronchial lung cryobiopsy (TBLC) in the diagnosis of diffuse parenchymal lung disease (DPLD) has shown a promising yield in recent times, with low post-procedural mortality and morbidity.
Objectives. To compare the yield of TBLC and conventional transbronchial forceps lung biopsy (TBLB).
Methods. A prospective study was carried out in patients with DPLD over a period of 1 year in a tertiary respiratory care institute in New Delhi, India. All 87 patients enrolled underwent both TBLB and TBLC. The procedures were performed in the bronchoscopy suite under conscious sedation and local anaesthesia, with an attempt to take a minimum of three biopsy specimens by conventional TBLB followed by TBLC. A 1.9 mm cryoprobe with a freezing time of 4 - 5 seconds was used. An Arndt endobronchial blocker was used to control bleeding along with locally administered medications.
Results. TBLB and TBLC led to a definitive diagnosis in 27 (31.0%) and 69 (79.3%) cases, respectively. The commonest diagnoses were hypersensitivity pneumonitis, sarcoidosis and pulmonary tuberculosis. TBLC led to additional diagnoses in 42 cases (48.3%). Pneumothorax was observed in 12 cases (13.8%), and moderate bleeding occurred in 63 (72.4%). There were no procedure-related deaths.
Conclusion. TBLC had a better diagnostic yield than conventional TBLB in DPLD. It has the potential to become a safe day-care procedure in a resource-limited setting, if certain precautions are taken.
Keywords. Diffuse parenchymal lung disease, transbronchial forceps lung biopsy, transbronchial lung cryobiopsy, bleeding, pneumothorax.

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Study synopsis
What the study adds. Compared with transbronchial forceps lung biopsy, transbronchial lung cryobiopsy (TBLC) led to additional diagnoses in 42 (48.3%) of 87 patients with clinicoradiological features of diffuse parenchymal lung disease. Pneumothorax was observed in 12 cases (13.8%) and moderate bleeding in 63 (72.4%). TBLC without rigid bronchoscopy or advanced airway devices under conscious sedation had a good diagnostic yield with an acceptable adverse events profile.
Implications of the findings. TBLC under conscious sedation is not resource intensive and can be carried out in settings with limited resources.

Diffuse parenchymal lung disease (DPLD) is a heterogeneous group of >200 pulmonary disorders that have been classified into numerous subtypes based on their clinical, radiological and histopathological profiles.[1-3] The diagnostic yield of conventional fibreoptic bronchoscopy-guided transbronchial forceps lung biopsy (TBLB) is variable and influenced by factors such as the size of the sample harvested, the presence of crush artifacts and operator expertise.[3] TBLB yield is relatively good in bronchocentric disease such as sarcoidosis, hypersensitivity pneumonitis (HSP), and malignancies such as lymphangitis and bronchoalveolar cell carcinoma. However, its yield decreases in cases of peripheral pathologies and pathologies with spatial heterogeneity such as usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP). Surgical lung biopsy remains the gold-standard procedure for tissue collection in DPLD, but it cannot be performed in many patients owing to respiratory impairment and medical comorbidities. It is performed in the operating room under general anaesthesia and requires mandatory insertion of an endotracheal tube. In recent years, transbronchial lung cryobiopsy (TBLC) has emerged as a useful alternative with a good diagnostic yield. In a comparison of complications following video-assisted thoracoscopic surgical lung biopsy and TBLC by Ravaglia *et al.*,[4] TBLC was associated with fewer days of hospitalisation than surgical lung biopsy (2.6 v. 6.1; $p<0.001$), and 1 of 297 patients (0.003%) died in the TBLC group compared with 4 of 250 (0.016%) in the surgical lung biopsy group.

However, few studies have compared the diagnostic yield of TBLC and surgical lung biopsy.

TBLC has met the need to obtain sufficient lung tissue for diagnosis with relatively few complications. In most studies of TBLC, advanced airway protection, rigid bronchoscopic intubations and fluoroscopy-guided probe placement have been used. In the present study, we aimed to investigate the diagnostic efficacy and safety of TBLC using a simpler combination of a flexible bronchoscope and an Arndt endobronchial blocker without the above resource-intensive techniques.

Methods

This was a prospective, single-centre, comparative observational study conducted over a period of 1 year in the bronchoscopy suite at a tertiary respiratory care institute in New Delhi, India. Informed written consent was obtained from the patients before each procedure, in the language of their choice. Exclusion criteria included thrombocytopenia, coagulation disorders, and clinical conditions that contraindicate bronchoscopy as per the British Thoracic Society (BTS) guideline.[5] The study protocol was approved by the institute ethical committee (ref. no. NITRD/PGEC/2017/6109).

Patients with clinicoradiological features of DPLD were initially evaluated by a team comprising pulmonologists and radiologists to determine the need for lung biopsy. A detailed clinical history was taken, including exposure to drugs and pets, occupational exposures and a smoking history, and a chest radiograph and a high-resolution computed tomography (HRCT) scan of the thorax were done. Routine blood tests, including a total leucocyte count, platelet count and measurement of the prothrombin time, were done.

All procedures were done in the bronchoscopy suite, without an anaesthetist present. Anticoagulants were withheld for an appropriate length of time prior to the procedure. The biopsy site was determined according to the maximum abnormality seen on the HRCT scan.

The analgesia and sedation protocol used was as follows:

- Patients were nebulised for 5 minutes with 3 mL 4% lignocaine with 2 mL normal saline, 10 minutes before the procedure.
- Three to five sprays of 10% lignocaine were used for pharyngeal anaesthesia. Loss of the gag reflex was taken as indicating adequate anaesthesia.
- Injections of 2 mg midazolam and 25 µg fentanyl were given initially at the start of the procedure.
- Lignocaine 1% was used in 1.5 - 2 mL aliquots in a spray-as-you-go technique. The working channel of the bronchoscope was used for administration.
- Additional injections of 0.5 mg midazolam were given according to the patient's condition. Top-ups were provided if the patient showed signs of discomfort such as excessive coughing or restlessness, up to a cumulative dose of 5 mg.
- A CO_2 monitor was not used. The pulmonologist monitored sedation by clinical assessment, using clinical signs such as heart rate, blood pressure, level of consciousness and pupil size.

Supplemental oxygen was provided via nasal prongs. Procedures were done without using any artificial airway or assisted ventilation. A fibreoptic bronchoscope was used (Fujinon, model no. EB-530T; Fujifilm, Japan). TBLB and TBLC were done sequentially. A flexible cryoprobe of size 1.9 mm diameter and 900 mm length was used (Erbecryo; Erbe Elektromedizin GmbH, Germany). Pulse rate, blood pressure, oxygen saturation and the electrocardiogram were monitored prior to and throughout the procedure.

Patients were kept nil per month before the procedure (2 hours for liquids and 4 hours for solids). The fibreoptic bronchoscope (inner working diameter 2.8 mm) was introduced orally through a mouth guard. An 9F Arndt endobronchial blocker (Cook Medical, USA) was hooked along with the bronchoscope and advanced through the airway. The Arndt blocker was then freed from the bronchoscope at the opening of the lobar bronchus that we planned to biopsy. Fig. 1 shows the Arndt blocker hooked onto the bronchoscope and the view inside the airways. The airways were inspected. Biopsy forceps were advanced through the working channel, and biopsy material was collected in saline water. The Arndt blocker was inflated whenever bleeding was encountered.

After checking the freezing time of the cryoprobe (1.9 mm) by dipping its tip in sterile water, it was advanced through the working channel in a similar way to forceps. When the probe reached the pleura, it was retracted by 1 cm and freezing was done for 4 - 6 seconds. The bronchoscope along with the cryoprobe was then immediately retracted, and the biopsied material collected in saline water. The Arndt blocker was inflated by 5 cm of air and the bronchoscope was reintroduced to check for any bleeding and to check the position of the inflated Arndt blocker, after which the Arndt blocker was deflated. Biopsy specimens were transferred to the pathologists in a formalin container for further processing. A chest radiograph was done 2 hours after completion of the procedure to rule out pneumothorax. For both TBLB and TBLC, an attempt was made to take a minimum of three biopsy specimens, preferably from different sites, as far as was possible in terms of patient parameters such as oxygen saturation, haemodynamics and bleeding. Bleeding associated with the procedure was quantified as none, mild, moderate or severe according to the BTS guideline on flexible bronchoscopy.[5] Haematoxylin and eosin-stained slides were reviewed by the pathologists. Diagnoses were made after multidisciplinary discussion (MDD) involving pulmonologists, pathologists and radiologists. As per the study protocol, all patients

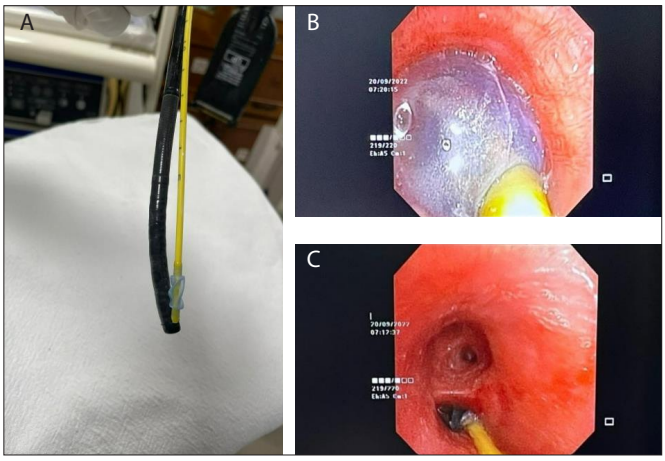

Fig. 1. (A) Hooking of the Arndt blocker on the bronchoscope, (B) scope view with the Arndt blocker inflated, and (C) scope view with the Arndt blocker deflated.

underwent TBLC, not only those who were unfit for surgical lung biopsy.

Patient data were entered into SPSS (Statistical Package for the Social Sciences) version 21 (IBM, USA), and qualitative and quantitative analysis was done. A *t*-test for means and proportions was done when required, with $p<0.05$ taken to be significant.

Results

A total of 87 patients were enrolled in our study after informed consent had been obtained. The characteristics of the study population are set out in Table 1. The most common site of transbronchial lung biopsy was the right lower lobe (*n*=60; 69.0%), followed by the left lower lobe (*n*=18; 20.7%) and the right middle lobe (*n*=9; 10.3%). The mean (standard deviation) numbers of biopsy samples taken by conventional TBLB and TBLC were 3.1 (0.61) and 2.17 (0.7), respectively. The macroscopic and microscopic features of the biopsy specimens obtained are described in Table 2. The TBLC specimens were significantly larger in size than those obtained by conventional TBLB ($p<0.0001$; *t*-test). Crush artifacts were found in none of the TBLC specimens, but were detected in 51 (58.6%) of the TBLB samples. The diagnostic yield of TBLB in our study was 31.0% (*n*=27), and that of TBLC was 79.3% (*n*=69). The final histopathological diagnoses are listed in Table 3. The same histopathological diagnosis was obtained by TBLC and TBLB in 27 patients. TBLC led to additional diagnoses in 42 patients (48.3%), while 18 (20.7%) had inconclusive reports for both the procedures. The most common diagnoses were pulmonary sarcoidosis, pulmonary tuberculosis (PTB) and HSP. UIP was diagnosed in 6 patients, only with TBLC. Forceps TBLB was associated with mild bleeding in the majority of cases (*n*=57; 65.5%), while with TBLC the majority had moderate bleeding (*n*=63; 72.4%). In those patients with a confirmed histopathological diagnosis, the MDD diagnosis was the same. For the rest (20.7%), in whom the histopathological diagnosis was uncertain, MDD diagnoses were deferred. They were referred to the thoracic surgeons for work-up for surgical lung biopsy. Pneumothorax was a complication in 12 patients (13.8%). Eleven were managed conservatively with high-flow oxygen therapy, and 1 required placement of an intercostal tube, which was removed 3 days after the procedure. No patient experienced oxygen desaturation events during the TBLB procedure, but 30 patients (34.5%) experienced such events during TBLC. Seventy-two patients (82.8%) were fit to go home on the day of the procedure. There were no deaths in our study.

Discussion

It is often challenging to arrive at a specific diagnosis in a patient with DPLD. Without histopathological confirmation, it can be difficult to make a diagnosis by means of radiological features, clinical history and other biomarkers, because there are areas of overlap. Conventional TBLB has been found to provide insufficient samples and a poor diagnostic yield. Surgical lung biopsy is associated with significant morbidity and mortality. In recent years, TBLC has been shown to have a good diagnostic yield with relatively few complications and has emerged as a promising alternative to surgical interventions. In the present study, the diagnostic yield of TBLC was significantly higher than that of conventional TBLB (79.3% v. 31.1%). In a study by Ravaglia *et al.*,[6] a specific pathological diagnosis was achieved in 614/699 cases (87.9%). The most common diagnosis was UIP (37.5%), followed by NSIP or organising pneumonia (OP)/NSIP (9.4%) and OP (8.3%). In a study by Wälscher *et al.*,[7] a histopathological pattern diagnosis was possible in 80 cases (73.4%), with a nonspecific disease pattern seen in 29 (26.6%). The most common pathological diagnosis was NSIP, reported in 22 patients (20.2%), with UIP and smoking-related interstitial lung disease (ILD) each reported in 11 patients (10.1%). In a study by Kropski *et al.*,[8] the diagnostic yield of TBLC was 20/25 (80%), with UIP the most common diagnosis (*n*=7/25, 20.8%), bronchiolitis obliterans organising pneumonia, desquamative interstitial pneumonia, malignancy and drug-induced ILD being diagnosed in 2 cases each (8%) and HSP and constrictive bronchiolitis in 1 case each (4%). The diagnostic yield of TBLC in the present study was similar to that in the above studies, but the histopathological diagnoses differ. In these studies, idiopathic interstitial pneumonias (IIPs) such as NSIP, UIP and OP were more prevalent than in our study, in which the UIP pattern was seen in only 6.8% of patients. HSP and sarcoidosis were common diagnoses in our study (17.2%). This finding may be due to the fact that unlike the developed Western world, where IIP constitutes 65% of ILD, in India the commonest ILD diagnosed is HSP, accounting for ~47.3% of cases.[9,10] In our study, 17.2% of patients were diagnosed as having PTB after their

Table 1. Clinical characteristics of the patients (*N*=87)

	n* (%)
Age (years), mean (SD)	50 (14.5)
Male gender	45 (51.7)
Patients discharged on day of procedure	72 (82.8)
Smoking status	
Current smokers	18 (20.7)
Ex-smokers	12 (13.8)
Never smokers	57 (65.5)
Spirometry parameters, mean (SD)	
FVC (%)	69 (19)
FEV1 (%)	72 (22)
FEV1/FVC ratio	81.2 (9.2)
DLCO (%)	42 (16.8)
Exposure to offending agents (other than tobacco smoke)	
Birds or pets	6 (6.9)
Organic/inorganic dust	9 (10.3)
HRCT features	
Reticulonodular shadows	18 (20.7)
Consolidation	12 (13.8)
Bronchiectasis	9 (10.3)
Cyst	9 (10.3)
Cavity	3 (3.4)
Lymphadenopathy	15 (17.2)
Fibrosis	21 (24.1)
Ground-glass opacities	24 (27.6)
Honeycombing	27 (31.0)
Mosaic attenuation	3 (3.4)

SD = standard deviation; FVC = forced vital capacity; FEV1 = forced expiratory volume in 1 second; DLCO = diffusing capacity for carbon monoxide; HRCT = high-resolution computed tomography.
*Except where otherwise indicated.

biopsy revealed necrotising granuloma. This was a learning experience for us, because in a tuberculosis-endemic country such as India, we should always keep an infectious cause in mind when a patient has radiological features suggestive of ILD. PTB shares many radiological features with sarcoidosis and HSP and may therefore masquerade as an ILD. The diagnosis becomes more difficult in an inadequately treated patient with PTB, because the clinical features in such cases are sometimes not prominent, and radiological evidence of fibrosis and/or lymphadenopathy may lead the physician to suspect an ILD.

With regard to complications, moderate bleeding was associated with TBLC in the majority (72.5%) of patients in the present study. Massive life-threatening bleeding did not occur in any patient. In the study by Ravaglia *et al.*,[6] moderate to severe bleeding was seen in 13% of patients, and no patient had a fatal haemorrhage. In the MULTICRIO study,[11] 6.5% of the 124 patients had moderate bleeding. Bleeding rates in our study were therefore considerably higher than in other contemporary studies, but bleeding was managed conservatively in all cases and no patient required intensive care unit admission. In a meta-analysis, Johannson *et al.*[12] found high levels of heterogeneity among studies reporting bleeding after TBLC (mean 26.6%, range 0 - 78%).[12] They postulated that the varying rates of bleeding may be due to differences in procedural technique (e.g. duration of freeze time, probe positioning), inconsistent definitions of adverse events such as bleeding, and differences in study populations. In our study, echocardiography was not part of the pre-procedure work-up. We suspect that undiagnosed pulmonary hypertension in some patients may have resulted in our relatively high rate of bleeding. The rate of pneumothorax in our study was 13.8%, which is similar to the pooled estimate of 12% (95% confidence interval 3 - 21) emerging from the meta-analysis by Johannson *et al.*[12] despite the fact that we did not use a fluoroscopy-guided biopsy technique. This finding is reassuring, because in a resource-limited country such as India, routine use of fluoroscopy may not always be feasible. Furthermore, none of our patients had a large air leak, as 11 pneumothoraces resolved on high-flow oxygen therapy and only 1 patient required intercostal tube placement with a 3-day hospital stay. Ravaglia *et al.*[6] found that cryobiopsies using a 2.4 mm probe were associated with increased rates of pneumothorax compared with 1.9 mm probes, but had similar diagnostic yields. We used the 1.9 mm probe in our study, which may have reduced the risk of pneumothorax while not decreasing the diagnostic yield. Pneumothorax is also dependent on the number of biopsy sites and the number of biopsy samples taken. However, there is no consensus regarding the optimal number of biopsies required for a confident diagnosis of ILD, or the number of biopsy sites or segments. Further studies are required in this area.

Our study had certain limitations. The sample size was small, and the study was conducted in a single institution. As both the procedures, TBLB and TBLC, were done in same setting, we could not attribute complications to a single procedure. Routine echocardiography and work-up for pulmonary hypertension were not done in our study, and these would have helped us to identify the patients with an increased risk of bleeding.

Table 2. Macroscopic and microscopic features of TBLB and TBLC specimens (*N*=87 patients)

	TBLB, *n* (%)*	TBLC, *n* (%)*
Diameter of biopsy sample (mm), mean (SD)	1.91 (0.964)	3.99 (1.78)
Histopathological findings		
Granuloma	9 (10.3)	18 (20.7)
Necrosis	3 (3.4)	15 (17.2)
Fibroblastic foci	21 (24.1)	30 (34.5)
Septal inflammation	15 (17.2)	30 (34.5)
Intra-alveolar macrophages	12 (13.8)	21 (24.1)
Z-N staining AFB	0	0
Alveolar tissue	21 (24.1)	66 (75.9)
Crush artifacts	51 (58.6)	0

TBLB = conventional transbronchial forceps lung biopsy; TBLC = transbronchial lung cryobiopsy; Z-N = Ziehl-Neelsen; AFB = acid-fast bacilli.
*Except where otherwise indicated.

Table 3. Final histopathological diagnoses in TBLB and TBLC biopsy samples (*N*=87 patients)

Diagnosis	TBLB, *n* (%)	TBLC, *n* (%)
Usual interstitial pneumonia	0	6 (6.8)
Hypersensitivity pneumonitis	3 (3.4)	15 (17.2)
Sarcoidosis	6 (6.8)	15 (17.2)
Idiopathic bronchiolocentric interstitial pneumonitis	3 (3.4)	3 (3.4)
Pulmonary Langerhans cell histiocytosis	3 (3.4)	3 (3.4)
Pleuroparenchymal fibroelastosis	0	3 (3.4)
Silicosis	3 (3.4)	3 (3.4)
Pulmonary tuberculosis	6 (6.8)	15 (17.2)
Nonspecific inflammation	3 (3.4)	3 (3.4)
Carcinoma	0	3 (3.4)
Inconclusive	60 (68.9)	18 (20.7)

TBLB = conventional transbronchial forceps lung biopsy; TBLC = transbronchial lung cryobiopsy.

Conclusion

Our study clearly shows that TBLC is a relatively safe procedure that can be performed in a day-care setting with a diagnostic yield much better than that of conventional TBLB. Head-to-head comparisons with surgical lung biopsy and TBLC should be done to ascertain the diagnostic yield of TBLC as opposed to surgical interventions.

Declaration. The research for this study was done in partial fulfilment of the requirements for KSM's DNB (Diplomate of National Board) in Respiratory Medicine degree at the National Board of Examinations, India.

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Author contributions. KSM, AC and ARW: patient enrolment and work-up, data entry, statistical analysis and manuscript preparation. JKS: formulation of the study, manuscript preparation and supervision of bronchoscopies. PS: manuscript preparation, data analysis and supervision of bronchoscopies. SM: histopathological examination of the biopsy samples, formulation of the study and manuscript preparation. RS: work-up of patients, manuscript preparation, conceptualisation and design of the study, and evaluating patients for surgical lung biopsy.

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Conflicts of interest. None.

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