Efficacy and safety of cryobiopsy versus forceps biopsy for interstitial lung diseases and lung tumours: A systematic review and meta-analysis

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ABSTRACT

Forcible biopsy (FB) is the most commonly used diagnostic tool for lung pathologies. FB is associated with a high diagnostic failure rate. Cryobiopsy (CB) is a novel technique providing a larger specimen size, few artefacts, more alveolar parts and superior diagnostic yield. CB, however, has drawbacks such as higher bleeding and pneumothorax rate. We conducted a meta-analysis to investigate the specimen area, diagnostic rate and bleeding severity in CB versus FB in interstitial lung diseases (ILDs) and lung tumours. A systematic literature search of PUBMED, BIOSIS PREVIEW and OVID databases was conducted using specific search terms. Eligible studies including RCTs and non-RCTs comparing cryobiopsy/cryotransbronchial biopsy (CB/CTBB) and forceps biopsy/forceps transbronchial biopsy (FB/FTBB) for specimen area, diagnostic rate and bleeding rate in ILDs and lung tumours were analysed. Two reviewers independently extracted data and evaluated the quality of the studies.

Eight studies involving 916 patients were analysed. Specimen area (mm²) was significantly larger in CB/CTBB than FB/FTBB (standard mean difference = 1.21, 95% confidence interval (0.94, 1.48), \( P = 0.00001 \)). The diagnostic rate was significantly higher in CB/CTBB than FB/FTBB (Risk ratio 1.36, 95% confidence interval (1.16, 1.59), \( P = 0.00002 \)). Three studies compared the bleeding severity with only one showing significantly more bleeding in CB. Cryobiopsy/cryotransbronchial shows superiority to FB/FTBB for specimen area and diagnostic rate. CB/CTBB has better efficacy over FB/FTBB.

Key words: cryobiopsy, forceps biopsy, interstitial lung disease, lung tumours, meta-analysis.

Abbreviations: CB, cryobiopsy; CBB/CTBB, cryobiopsy/cryotransbronchial biopsy; CI, confidence interval; FB, forceps biopsy; FB/FTBB, forceps biopsy/forceps transbronchial biopsy; ILDs, interstitial lung diseases; RCT, Randomized controlled trial; SLB, surgical lung biopsy.

INTRODUCTION

Flexible bronchoscopy with forceps biopsy (FB) is the most frequently used tool to obtain specimens for pathologic analysis. The sensitivity of FB is approximately 74% for endobronchial tumours. Gellert et al. reported that at least five specimens were required to attain a probability greater than 90% of obtaining at least one positive sample. Combining FB with other methods such as needle aspiration, bronchial alveolar lavage cytology and brush cytology improves the yield up to 89.5%. However, these combined cytology methods increase operative time and overall cost. A definitive diagnosis is often not possible after histological analyses of the samples obtained by FB, because of the presence of artefacts, small amount of alveolated tissue and small size. Therefore, more aggressive, costly techniques are frequently employed. Surgical lung biopsy (SLB) is recommended for interstitial lung diseases according to the 2011 American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association consensus statement. SLB has a mortality of 3–4% at 30 days, risks exacerbation of underlying lung disease as well as infection, prolonged air leak (6.2%), and 57% of patients were reported to complain of continuing pain after 7–12 months at the biopsy site.

Recently, cryotechnology has been utilized for several therapeutic purposes in bronchology including endobronchial cryodebridement procedures for endobronchial tuberculosis, tracheal strictures, endobronchial fibrosis, removal of broncholith, cryosurgery for lung cancer and in immediate debulking of endobronchial tumours (cryorecanalization). Cryosurgical equipment operates by the Joule–Thomson effect, where a compressed gas released at high flow rapidly expands and creates a very low temperature at the tip of the probe. Cryorecanalization involves the use of the cryoadhesion technique. Samples obtained from cryorecanalization revealed extraordinarily well-preserved tissue samples, larger in size, less artefacts and mostly vital tumour. This technique has transformed the biopsy of endobronchial lesions and marked the introduction of a new sampling technique (cryobiopsy (CB)) for bronchoscopists.

Cryobiopsy has been used to diagnose interstitial lung diseases (ILDs), lung tumours, peripheral...
The specimens obtained from CB meet the required characteristics of a specimen for histopathology, large size, absence or few artefacts, more alveolar tissue and a higher diagnostic yield. An increase in bleeding rate and pneumothorax rate has been suggested by Pajares et al. and multiple case series, but these studies are limited by sample size and study design. Hence, the need for a meta-analysis is critical.

To the best of our knowledge, there is no meta-analysis on the efficacy and the safety of CB. We performed a meta-analysis in order to obtain a clearer answer on the pros/cons of cryobiopsy/cryotransbronchial biopsy (CB/CTBB) versus forceps biopsy/forceps transbronchial biopsy (FB/FTBB).

METHODS

Eligibility criteria
Inclusion criteria were all studies in which CB/CTBB was compared with FB/FTBB in ILDs, endobronchial and peripheral lung tumours were included. RCTs, cohort studies, retrospective studies and non-RCTs were considered. Exclusion criteria were studies involving less than 10 subjects, non-comparative single-arm studies and studies investigating CB for other pathologies. Studies comparing CB/CTBB with techniques other than FB/FTBB were also not considered. We did not have any restriction on the publication year, language, country and set-up in which a study was performed.

Search and selection of the studies
A comprehensive literature search was employed in order to perform a systematic review of the available evidence. This included searching the following databases: PUBMED, BIOSIS and OVID. The last search was performed in May 2015. The search strategy (Cryobiopsy OR Cryoprobe biopsy OR Cryotransbronchial biopsy) AND (Interstitial lung diseases OR Diffuse parenchymal lung diseases OR Lung tumor) was employed. The lists of references of included articles were hand searched. The titles and abstracts of the search results were screened independently by two review authors. Potential articles underwent full text review.

Data extraction
Two independent reviewers abstracted the data in a standard format. The following information was sought from each article: first author, year of publication, diseases suspected, type of study, specimen area, diagnostic rate and bleeding severity. Discrepancies in data extraction were resolved by consensus, referring back to the original article and by contacting the study authors. Details of the included studies are summarized in Table 1.

Quality assessment
The risk of bias was evaluated by two reviewers independently as per Cochrane Handbook for Systematic Reviews of Intervention (v5.1.0) (Higgins 2011). Each reviewer checked the choices of the other. Disagreements were settled by consensus. The summary assessments of the risk of bias within studies were categorized as ‘low risk of bias’, ‘unclear risk of bias’ or ‘high risk of bias’.

Outcome evaluated
The outcomes evaluated were specimen area, diagnostic yield and bleeding severity.

Data analysis
We identified four studies for specimen area (given in mm²). We calculated the mean and standard deviation according to Xiang Wan et al. when only the median and range were documented in the studies. Seven studies compared the diagnostic yield. The bleeding severity was described differently in three studies. The data could not be pooled. A qualitative analysis was performed.

RevMan v5.3 provided by Cochrane Coordination Net was used to carry out the meta-analysis. For continuous variables, we used standardized mean difference (SMD), inverse variable statistical method and fixed effect models. For categorical variables, we used relative benefit as the effect measure, Mantel-Haenszel statistical method and fixed effect model. In case P < 0.10, random effect meta-analysis was carried out. Both effect measures were expressed with a 95% confidence interval (CI). The I² statistic was first calculated to assess the heterogeneity among the proportions of the included studies. If the P value was less than 0.10 and I² was greater than 50%, the assumption of homogeneity was deemed invalid, and subgroup analysis was employed to explore the heterogeneity.

RESULTS

Search results and characteristics of included studies
The search results are summarized in Figure 1. Eight studies (four RCTs, two cohorts and two retrospective studies) were involved, comprising 916 subjects. Intervention measures: We analysed the specimen area in four studies, diagnostic rate in seven studies and bleeding severity in three studies.

Quality assessment of trials
Four RCTs and four non-RCTs are included in this meta-analysis. Only one RCT used sealed-numbered envelopes for randomization. The remaining three trials have not stated the method of randomization, which we categorized as ‘unclear risk of bias’. None of the trials used a distribution concealing method. No blinding of participants and personnel was used in any trial. In two trials, the histopathologists were blinded for sample analysis. There was no blinding.
<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Number of subjects</th>
<th>Disease involved</th>
<th>Type of study</th>
<th>Specimen size</th>
<th>Diagnostic rate (%)</th>
<th>Blending rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Babiak</td>
<td>2009</td>
<td>41—all subjects, FB and CB</td>
<td>ILDs</td>
<td>Retrospective</td>
<td>15.11 mm² (2.15–54.15 mm²)</td>
<td>95.12</td>
<td>58.53 CB FB</td>
</tr>
<tr>
<td>Schumann C.</td>
<td>2010</td>
<td>First 55—all subjects, FB and CB</td>
<td>Lung tumours</td>
<td>Randomized cohort</td>
<td>10.4 mm²</td>
<td>89.1</td>
<td>65.5</td>
</tr>
<tr>
<td>Aktas A.</td>
<td>2010</td>
<td>41—all subjects, CB and FB</td>
<td>Lung tumours</td>
<td>Prospective clinical trial</td>
<td>0.8 cm (0.3–4.0 cm)</td>
<td>92.7</td>
<td>78 CB FB</td>
</tr>
<tr>
<td>Griff</td>
<td>2011</td>
<td>33—15, CB; 18, FB</td>
<td>ILDs</td>
<td>Prospective clinical trial</td>
<td>17.1 ± 10.7 mm²</td>
<td>95</td>
<td>85.1 CB FB</td>
</tr>
<tr>
<td>Hetzel J.</td>
<td>2012</td>
<td>563—282, CB; 281, FB</td>
<td>Lung tumours</td>
<td>Randomized single blinded multicentre trial</td>
<td>11.17 mm²</td>
<td>95</td>
<td>85.1 CB FB</td>
</tr>
<tr>
<td>Schuhmann M.</td>
<td>2013</td>
<td>31—all subjects, CB and FB</td>
<td>Peripheral solitaryLung tumours</td>
<td>Randomized clinical trial</td>
<td>11.17 mm²</td>
<td>61.2</td>
<td>48.4</td>
</tr>
<tr>
<td>Chou C.L.</td>
<td>2013</td>
<td>75—all subjects, CB and FB</td>
<td>ILDs</td>
<td>Retrospective</td>
<td>13.8 ± 3.8 mm</td>
<td>100</td>
<td>69.3</td>
</tr>
<tr>
<td>Pajares</td>
<td>2014</td>
<td>77</td>
<td>ILDs</td>
<td>Randomized trial</td>
<td>14.7 ± 11 mm²</td>
<td>74.4</td>
<td>34.1 CB FB</td>
</tr>
</tbody>
</table>

CB, cryobiopsy; FB, forceps biopsy; ILDs, interstitial lung diseases.
of outcomes data in the other two trials. There were a low risk of blinding and detection bias in all four RCTs. Two studies reported dropouts and/or withdrawal and the numbers and reasons were given in details across trials (low-risk bias). No dropouts/withdrawal were reported in the other six studies. All results were reported. There were a low risk of attrition and selective reporting bias in all eight studies. The risk of bias in the four RCTs and four non-RCTs is shown in Figure 2.

**Specimen area**

Four studies (two RCTs, one cohort, one retrospective) were involved in comparing CB/CTBB and FB/FTBB for specimen size. Meta-analysis showed a significant statistical difference between CB/CTBB and FB/FTBB (SMD = 1.21, 95% CI (0.94, 1.48), \( P < 0.00001 \)). CB/CTBB gives larger samples than FB/FTBB. There was no heterogeneity detected across the studies (\( P \) of heterogeneity = 0.32, \( I^2 = 14\% \)). All data for specimen area are showed in Figure 3.

**Diagnostic rate**

Seven studies (four RCTs, two retrospectives, one cohort) compared the diagnostic rate with CB/CTBB and FB/FTBB. A total of 517 were diagnosed among 564 patients (91.67%) in CB/CTBB group compared with 411 among 562 patients (73.13%) in FB/FTBB group. Compared with FB/FTBB, CB/CTBB was associated with a significant increase in the diagnostic rate (Risk ratio (RR) 1.36, 95% CI (1.16, 1.59), \( P = 0.0002 \)). Heterogeneity was detected across trials by \( I^2 \) test (\( P \) of heterogeneity < 0.0001, \( I^2 = 79\% \)). In this meta-analysis, we included two pathologies, ILDs and lung tumours. Subgroup analysis was carried out. There existed no heterogeneity in ILD subgroup (\( P \) of heterogeneity = 0.27, \( I^2 = 18\% \)). For lung tumours subgroup, heterogeneity was detected (\( P \) of heterogeneity = 0.01,
I2 = 69%). I2 test for subgroup differences revealed heterogeneity (P of heterogeneity = 0.006, I2 = 86.5%). This implies there were significant differences in the characteristic of the two subgroups accounting for the heterogeneity. All the statistical analyses are shown in Figure 4.

Bleeding severity

Three studies reported bleeding severity. The bleeding incidence in CB/CTBB was 86/361 (23.76%), and that of FB/FTBB was 75/360 (20.83%). The results are summarized in Table 2. In two studies,13,17 no significant difference in bleeding severity was reported (Aktas, P > 0.05; Pajares, P = 0.068). Hetzel et al. showed significantly more bleeding with cryobiopsy compared with forceps biopsy (P = 0.009).18

Reporting bias

We did not perform a funnel plot as they were only eight studies and there was considerable heterogeneity between the outcomes.

DISCUSSION

We systematically evaluated eight studies including four RCTs and four non-RCTs for efficacy (specimen area and diagnostic yield) and safety (bleeding severity) of CB/CTBB versus FB/FTBB.

Diagnosis of ILDs requires a clinic-patho-radiological approach, which is usually carried out by a multidisciplinary team. In certain cases, clinical and imaging features are sufficient to establish a diagnosis. Additional procedures, including FB, transbronchial lung biopsy and SLB are needed to have a confirmatory diagnosis for certain cases. According to the ATS/ERS guidelines, SLB is the gold standard for diagnosis if classic imaging criteria are not met mostly because it provides larger specimen size. The procedure requires general anaesthesia and mandates hospitalization with a chest tube in place. Because of these complications, many clinicians perform transbronchial FB. In a study of 801 diffuse parenchymal lung disease patients undergoing FB, less than one-third of biopsy specimens had a confirmatory diagnosis.25 The inadequate and non-diagnostic sample obtained by transbronchial FB were mostly due to the small specimen size and presence of crush artefacts.26 The presence of adequate alveolated tissue is crucial for diagnosis. Fraire A.E. et al. reported that a greater percentage of diagnosis of infection was made in patients whose specimens (from FB) contained greater than or equal to 20 alveoli (P = 0.01).27 CB is a novel technique providing larger specimen size,13,15 less crush artefacts,14,28 more viable lung parenchyma and more alveolated tissue,22 which can be beneficial in diagnosing and treating lung pathologies and immunohistochemical analysis. CB can potentially dispense the need of SLB in some cases. The potential advantages including specimen size and diagnostic rate have resulted in a growing
interest in clinicians, but the complications (bleeding and pneumothorax) have discouraged experts and patients to consider this novel technique. Many studies have reported the use of CB for diagnosis of lung pathologies, but only few studies have compared CB with FB.

In this meta-analysis, we found that specimen area in CB was significantly larger than in FB [SMD = 1.21, 95% CI (0.94, 1.48), P < 0.00001]. Griff et al. reported 73% alveolated tissue in CB compared with 56% in FB (P = 0.29). An artefact-free sample is necessary for a superior diagnostic yield. Schumann C. et al. reported the artefact-free tissue areas of each slide were considerably greater in CB than in FB (9.6 vs 3.6 mm², P < 0.001), giving a higher diagnostic rate in CB (89.1%) versus FB (65.5%) (P < 0.05). A multicentre trial including 563 patients reported a higher diagnostic yield of 95% in CB compared with 85.1% in FB (P < 0.001). This meta-analysis confirmed that the diagnostic rate by CB is superior to FB (RR 1.36, 95% CI (1.16, 1.59), P = 0.0002). According to the subgroup analysis, the relative benefit of CB is greater in ILDs (RR 1.77, 95% CI (1.34, 2.32), P < 0.0001) compared with lung tumours (RR 1.25, 95% CI (1.10, 1.43), P = 0.0009).

**Table 2** Qualitative analysis of bleeding severity

<table>
<thead>
<tr>
<th>Author</th>
<th>Definition of bleeding as per study</th>
<th>Number of patients in CB, n (%)</th>
<th>Number of patients in FB, n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aktas et al., (n = 41); All performed CB and FB; CB = 41, FB = 41</td>
<td>No bleeding 26 (63.4) 27 (65.9)</td>
<td>Simultaneous bleeding 5 (12.2) 5 (12.2)</td>
<td>Mild: cold water + adrenaline 8 (19.5) 9 (21.9)</td>
<td>Moderate: APC application 2 (4.9) 0 (0)</td>
</tr>
<tr>
<td>Hetzel et al., (n = 563); CB = 282, FB = 281</td>
<td>No bleeding 59 (19.9) 91 (30.6)</td>
<td>Mild: suctioning 183 (61.8) 153 (51.5)</td>
<td>Severe: ice cold saline, diluted vasoconstrictive drug, balloon tamponade, APC, MV, conversion to rigid bronchoscope. 54 (18.2) 53 (17.8)</td>
<td></td>
</tr>
<tr>
<td>Pajares et al., (n = 77); CB = 39, FB = 38</td>
<td>Grade 0: no bleeding 5 (12.8) 8 (21.1)</td>
<td>Grade 1: suction 12 (30.8) 17 (44.7)</td>
<td>Grade 2: occlusion, use of endoscopic procedures and/or ice cold saline 22 (56.4) 13 (34.2)</td>
<td>Grade 3: haemodynamic compromise, admission to ICU 0 (0) 0 (0)</td>
</tr>
</tbody>
</table>

APC, argon plasma coagulation; CB, cryobiopsy; FB, forceps biopsy; ICU, intensive care unit; MV, mechanical ventilation.

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**Figure 4** Diagnostic yield of cryobiopsy versus forceps biopsy. Fixed effects model of risk ratio (95% confidence interval). Events—number of patients diagnosed using this technique. Total—number of patients undergoing this technique.
There were only three studies analysing bleeding. It was not possible to pool the results because of heterogeneity in the grading of bleeding severity. Two studies showed no significant difference in bleeding severity. However, the sample sizes were smaller than Hetzel (n=563). We need more RCTs assessing bleeding severity in a standardized way. Pajares et al. reported a moderate bleeding of 56.4% in CB compared with 34.2% in FB. No mortality and no hemodynamic instability were reported because of bleeding. Iced cold saline, diluted vasoconstrictive agents, electrocau, and Fogarty balloon should be available in a centre undergoing CB as a diagnostic tool, as these can aid in controlling bleeding. A secure airway using endotracheal tube, rigid bronchoscope, laryngeal airway mask or igel airway can be used to re-insert the bronchoscope more easily to suction and control any bleeding. In a large series of 300 participants, Gershmann et al. have analysed the safety profiles of CB/CTBB and FB/FTBB. The series reported no significant difference in bleeding rate between the two groups with a rate of 5.2% in CB/CTBB compared with 4.5% in FB/FTBB (P=0.706). Pneumothorax rate in CB could not be analysed systematically because of insufficient data from the literature. Pajares et al. reported 7.7% pneumothorax rate in CB compared with 5.2% in FB. Gershmann et al. have also shown no significant difference in pneumothorax rate (4.95% in CB/CTBB and 3.15% in FB/CTBB, P=0.303). In a study of 69 patients undergoing CB, Casoni et al. reported 28% pneumothorax rate. CB can be performed under fluoroscopic guidance maintaining 1–2 cm distance from the probe tip to the chest wall. This can help in preventing pneumothorax rate.

Our meta-analysis has limitations as we have combined studies involving peripheral and endobronchial lesions. Endobronchial lesions are visible, making them easier to biopsy than peripheral lesions. Bleeding is easier to control in endobronchial lesions. Biopsy of peripheral lesions are also guided by endobronchial ultrasound and imaging. This can add a source of error. However, because of the limitations of studies of peripheral lesions, we have combined endobronchial and peripheral lesions to analyse the efficacy and safety of cryobiopsy. More RCTs of peripheral lesions are required to provide higher level of evidence. More well-designed RCTs, multicentre trials investigating diagnostic rate, bleeding severity, pneumothorax and artefacts free tissue are needed to provide more evidence for efficacy and safety of CB.

In conclusion, this meta-analysis demonstrated that CB/CTBB is a more efficient diagnostic tool with superior diagnostic rate and larger specimen area than FB/FTBB. No meaningful conclusion could be drawn regarding bleeding severity. More studies of peripheral lesions are required with well-graded bleeding severity in order to further evaluate bleeding severity in CB. CB can be used as an effective and safe diagnostic tool in clinical practice for ILDs and lung tumours. More RCTs and multicentre trials of peripheral lesions are required to analyse the safety and efficacy of CB for higher level of evidence.

REFERENCES


