EXECUTIVE SUMMARY
(Adapted from the report by SYFUL AZLIE MD FUZI)

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Background

The current approach to the diagnosis and management of interstitial lung disease (ILD) includes a multidisciplinary discussion undertaken by clinicians, radiologists, and pathologists. Adequate lung biopsies (qualitatively and quantitatively) are essential contributors to the diagnosis when high resolution computed tomography (HRCT) findings as well as clinical and laboratory data are insufficient. Historically, surgical lung biopsy (SLB) either through open surgery or video-assisted thoracoscopic surgery (VATS) has been considered as the definitive means of obtaining adequate biopsy specimens. However, in many patients, the risk-benefit ratio of the procedure is unacceptable. Morbidity and mortality related to SLB are substantial, particularly in older subjects, in patients with significant comorbidities or severe respiratory impairment, and in cases with a final diagnosis of idiopathic pulmonary fibrosis (IPF). Conventional transbronchial biopsy with forceps on the other hand has a very poor diagnostic yield and insufficient in terms of size of the histological samples. Transbronchial lung cryobiopsy (TBLC) has therefore been proposed as an alternative bronchoscopic technique for histological sampling in patient with ILD, potentially combining the higher yield of SLB with the lower complication rate of transbronchial forceps biopsy. Despite a substantial and expanding body of literature, the diagnostic usefulness and safety of TBLC remains to be defined. Hence, this technology review was requested by Senior Consultant Pulmonologist from Serdang Hospital to evaluate if TBLC can be suggested as a first line procedure in patient with ILD instead of SLB.

Objective

To identify and evaluate evidence on diagnostic accuracy/ performance, safety, organisational aspects, and economic implication related to TBLC in patient with ILD.

Methods

A systematic review was conducted. Review protocol and search strategy was developed by the main author and *Information Specialist*. The following electronic databases were searched through the Ovid interface: Ovid MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE® 1946 to 13th November 2020, EBM Reviews - Health Technology Assessment (4th Quarter 2016), EBM Reviews - Cochrane Database of Systematic Review (2005 to 13th November 2020), EBM Reviews - Cochrane Central Register of Controlled Trials (October 2020), EBM Reviews – Database of Abstracts of Review of Effects (1st Quarter 2016), and EBM Reviews - NHS Economic Evaluation Database (1st Quarter 2016). Parallel searches were run in PubMed, US FDA and INAHTA database. No limits were applied to the search. Additional articles were identified from reviewing the references of retrieved articles. The last search was performed on 4th January 2021.

Results and conclusion:

Diagnostic accuracy/ performance

There was substantial fair level of retrievable evidence to suggest that the diagnostic yield of TBLC in ILD varies from 79.0% to 91.7%, and is greater than conventional transbronchial forceps biopsy (56.5% to 73.1%) but lower than SLB (91.1% to 92.7%). Since the diagnosis of ILD is not based solely on histology but following multidisciplinary discussion, the yield was found to be either similar to, or greater than the histological diagnostic yield alone. With a sensitivity of 87.0% and

specificity of 57.0%, TBLC lags somewhat behind VATS, which has a relatively higher sensitivity and specificity (91.0% and 58.0%%, respectively). In light of the evidence, diagnostic yield was significantly influenced by the number of samples and the sampling strategy: improving dramatically when more than two samples were performed (instead of only one) and when biopsy was obtained in two different sites (instead of only one site), either from the same lobe or from different lobes. High levels of agreement between TBLC and SLB for both histopathological interpretation (70.8%; κ of 0.70) and multidisciplinary discussion diagnose (76.9% with a κ of 0.62) were also shown. The TBLC multidisciplinary discussion diagnosed made with high confidence were particularly reliable, showing excellent concordance with SLB multidisciplinary discussion diagnosis. Another aspect, size of samples obtained with TBLC was significantly bigger compared with flexible forceps biopsy (11.2-30.4 mm^2 versus 3.3-4.3 mm^2; $p<0.005$).

Safety

There was substantial fair level of retrievable evidence to suggest an appreciably lower rate of mortality in favour of TBLC (0.1% to 2.0%) as compared with SLB (1.8% to 2.3%). Available data indicate pneumothorax to be a major complication associated with TBLC with rate varies from less than 5.0% to almost 20.0%. Bleeding during cryobiopsy was common although there was no generally accepted bleeding severity scale and therefore comparability of different studies was difficult. Instead, the rate of bleeding (moderate to severe) following TBLC was found higher (0.3% to 39.0%) than forceps biopsy (10.1% to 20.8%). Considering the results, no cases of severe bleeding requiring suspension of the procedure were reported and no additional medical or surgical measures were needed to control bleeding.

Organisational issues

There was substantial fair level of retrievable evidence to suggest that TBLC is well tolerated and seems to be suitable as an outpatient procedure since most patients were discharged within one day, with mean operation time ranged from six to 35 minutes.

Economic implication

Transbronchial lung cryobiopsy has the potential to deliver significant cost savings as compared to SLB or VATS since it can be undertaken by respiratory physicians with interventional bronchoscopy skills in an endoscopy suite under conscious sedation without requiring thoracic surgeon, general anaesthesia, and a theatre team. Given this information, two studies on cost-analysis were retrieved. The first demonstrated potential savings of £210 per patient in the first year and £647 in subsequent years as compared with VATS based on actual UK National Health Service (NHS) financial data, 2015-2016 reimbursement tariffs, and results of the systematic review. Another study which based on the Spanish healthcare system also highlights an additional advantage of cryobiopsies over SLB. According to the figures, TBLC could save between €31,451.97 (€953.09 per patient) in the case of outpatient SLB, and €59,846.29 (€1,925.29 per patient) in the case of SLB with 48-hour admission, which is often the case in their region.