AABIP JOURNAL CLUB

Transbronchial Needle Aspiration Combined With Cryobiopsy in the Diagnosis of Mediastinal Diseases

The clinical question

Does endobronchial ultrasound guided transbronchial cryobiopsy (TBCB) increase the diagnostic yield of mediastinal lymph node sampling when used in conjunction with endobronchial ultrasound guided transbronchial needle aspiration (TBNA)?

Take home message

TBCB is a relatively safe technique of sampling mediastinal lymph nodes and may increase diagnostic yield when evaluating benign disease such as sarcoidosis, pneumoconiosis, or TB when used as an adjunct diagnostic tool with TBNA. Caution should be used in its evaluation of pulmonary malignancies as there does not appear to be any additional diagnostic yield.

Background

TBNA has long been central to the evaluation of potentially malignant and benign mediastinal lymphadenopathy. Limitations of TBNA include lack of architectural preservation and a potential limitation in tissue acquisition for genomic and immunohistochemical testing. Transbronchial cryobiopsy, historically utilized in the evaluation of parenchymal lung disease, has recently been implemented as an adjunct tool to TBNA in the evaluation of mediastinal lymph nodes but there is a need for further studies evaluating its safety and efficacy.

The American Thoracic Society, European Respiratory Society, and the American College of Chest Physicians currently recommend TBNA in the evaluation of pathologically enlarged mediastinal lymph nodes in the staging and evaluation of non-small cell lung cancer. There are no society guidelines regarding the use of TBCB in evaluating mediastinal lymph nodes. A recent systematic review of 7 studies totaling 555 patients found that the diagnostic yield of TBCB in addition to TBNA was higher than TBNA alone (92% vs. 80%). However, when evaluating diagnostic yield by specific etiologies, the addition of TBCB did not add any benefit in evaluating solid malignancies but did improve diagnostic evaluation of hematologic malignancies and benign etiologies.

Study Design

- **Study design:** Open Label Randomized Trial
- **Primary Outcome(s):** Diagnostic Yield – Defined as the proportion of participants for whom the biopsy samples led to a definitive positive or negative diagnosis.
- **Secondary Outcome(s):** Specimen adequacy and size, suitability of samples for molecular genetic assay, and duration of the bronchoscopic procedures.
- **Intervention(s):** The control group underwent EBUS-TBNA in the standard fashion using either 21 or 22-gauge needles with 4 passes through each node. The intervention group underwent EBUS with TBNA using a 21 or 22 gauge needle with 4 passes through the target lesion. Following this, a high-frequency electric needle knife was used to make a 2-3 mm incision in the tracheobronchial wall followed by EBUS guidance of a 1.1 mm cryoprobe and application of a single 7 second freeze cycle.

Population

Inclusion criteria

- Age 15
- At least 1 mediastinal lesion ≥ 1 cm on short axis
- Clinical Symptoms of cough, sputum production, or complicated parenchymal findings that would necessitate biopsy.

Exclusion criteria

- EBUS fails to identify a target lesion
- Mediastinal lesions are actually cysts or abscesses
- Potential need for other procedures apart from the mediastinal lymph node biopsy.

Baseline characteristics

- Male predominance (61%)
- Patients were only Asian or White
- The three most sampled lymph node stations were 7 (32%, 35%), 4R (17%, 22%), or 11R (11%,11%) for the patients in the TBNA alone and the TBNA-TBCB groups respectively.
- The mean short axis diameter the lymph nodes was 2.1 cm (Standard Deviation of 0.8).

Outcomes

Primary outcomes:

- The addition of TBCB significantly increased overall diagnostic yield for mediastinal lesions evidenced by 93% of the treatment group vs. 81% of the control group.

Secondary outcomes:

- In a subgroup analysis, there was no difference in yields for neoplastic lesions (94% vs. 91% p = 0.42) whereas there was an increase in yield when evaluating benign disease (94% vs. 64% p = 0.0004).
- In an intraindividual analysis, TBCB increased the diagnostic yield by 12% compared with TBNA alone, supporting the finds from the interindividual analysis.
- The mean diameter of the TBCB specimen was 3.8 mm (Standard Deviation of 1.1 mm)
- TBCB increased the specimen suitability for genomic testing and PDL1 immunohistochemistry testing (97% vs. 79% p = 0.033)

Funding

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Commentary

There have been approximately 7 other clinical trials to evaluate similar questions to this one but this is the first clinical trial to analyze the potential benefits and safety profile of adding TBCB to TBNA using both an interindividual and intraindividual analysis. The study benefits from this combination of interindividual analysis of the intervention and control groups as well as intra individual analysis as the intraindividual analysis adds a second layer of support for the investigator's findings. The trial's pre-specified technique of utilizing a single pass of the cryoprobe may limit the applicability of this technique to solid tumor metastatic disease evaluation as it does not allow for sampling of multiple sections of the lymph node potentially leading to false negative samples. Procedural times were 5 min longer ($p < 0.0001$) which may not make a practical difference when sampling one node however if multiple nodes are needed, this may significantly lengthen procedural duration. Additionally, as the investigators technique utilized a single pass of the cryoprobe, they do not have data regarding the feasibility and safety of doing multiple cryoprobe passes in terms of bleeding, pneumothorax, or pneumomediastinum. There is a potential signal to improved diagnostic yield in evaluating hematologic malignancies like lymphoma however the results were not statistically significant and would need further study.

Suggested reading

- Botana-Rial M, Lojo-Rodriquez I, Leiro-Fernandez V, Ramos-Hernandez C, Gonzalez-Montaos A, Pazos-Area L, Nunez-Delgado M, Fernandez-Villar A. Is the diagnostic yield of mediastinal lymph node cryobiopsy (cryoEBUS) better for diagnosing mediastinal node involvement compared to endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA)? A systematic review. Respiratory Medicine. 2023;218:107389. doi:10.1016/j.rmed.2023.107389

- Troy LK, Williamson JP. Mediastinal cryobiopsy: safe and effective but in whom and when? Lancet Respiratory Medicine. 2023; 11(3):217-219 DOI: 10.1016/S2213-2600(22)00410-6

- Mondoni M, Sotgiu G. Optimizing the endoscopic diagnosis of mediastinal lymphadenopathy: a glimpse on cryobiopsy. BMC pulmonary medicine. 2022;22(1):355. https://doi.org/10.1186/s12890-022-02160-2

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