A Randomized Trial Evaluating the Effect of 10 versus 20 Revolutions Inside the Lymph Node on the Diagnostic Yield of EBUS-TBNA in Subjects with Sarcoidosis

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Keywords

Endosonography · EBUS-TBNA · Tuberculosis · Granuloma

Abstract

Background: Endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA) is the preferred modality for sampling intrathoracic lymph nodes in patients with suspected sarcoidosis. Whether the number of revolutions of the needle inside the lymph node while performing TBNA affects the diagnostic yield is unknown. **Objectives:** The aim of this paper was to compare the yield of different numbers of needle revolutions (10 vs. 20) during EBUS-TBNA in sarcoidosis. **Methods:** Consecutive subjects with a clinico-radiological suspicion of sarcoidosis were randomized 1:1 to undergo EBUS-TBNA with either 10 (group 1) or 20 revolutions (group 2). The primary and secondary outcomes were the diagnostic yield and adequacy of aspirates, respectively. Other outcomes were procedure duration, gross blood contamination of the aspirates, and safety of the procedure. **Results:** Of the 171 subjects screened, 150 (mean age 43.5 years; 47.3% women) were randomized. A mean of 2.8 (group

1: 2.8, group 2: 2.7; $p = 0.37$) lymph nodes were sampled per subject with a mean of 2.1 passes per node in each group ($p = 0.60$). Among 133 subjects finally diagnosed with sarcoidosis, there was no difference ($p = 0.65$) in the diagnostic yield of EBUS-TBNA between group 1 (52/65, 80.0%) and group 2 (57/68, 83.8%). Adequate aspirates were obtained in 96.9 and 97.1% of the subjects in groups 1 and 2, respectively ($p = 1.00$). There was no difference in the procedure duration, the proportion of subjects with grossly bloody specimens, or complications between the 2 groups. **Conclusions:** The diagnostic yield and specimen adequacy were not different when EBUS-TBNA was performed with 10 or 20 revolutions in subjects with sarcoidosis.

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Introduction

Sarcoidosis is a systemic granulomatous disorder of an unknown cause [1]. As it most often involves the lungs and lymph nodes, these 2 sites are frequently accessed for a histologic diagnosis of the disease. Presently, endobron-

chial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA) is extensively used for sampling intrathoracic lymph nodes in patients suspected to have sarcoidosis. Because of its high yield and excellent safety, EBUS-TBNA has gradually supplanted other modalities such as conventional TBNA and mediastinoscopy for this purpose [2–5]. The pooled yield of EBUS-TBNA in sarcoidosis is 79% (range, 54–93) [6]. When combined with endobronchial biopsy (EBB) and transbronchial lung biopsy (TBLB), the yield may be as high as 92% [7–9].

Due to the wide variation in the diagnostic yield of EBUS-TBNA in subjects with sarcoidosis [6, 10], an important question arises, whether certain technical aspects of the procedure affect the yield. In this context, several factors such as the number of lymph nodes sampled, number of passes made, use of a larger bore (19G and 21G vs. 22G) aspiration needle, and the utilization of rapid onsite evaluation (ROSE) have been investigated [8, 9, 11–13]. However, more research is required to delineate the utility of several other technical aspects of the procedure, and a call has been made for the same by 2 international societies [14, 15]. While performing EBUS-TBNA, the needle is used to puncture a lymph node under real-time ultrasonographic guidance. Subsequently, back and forth movements of the needle (referred to as revolutions, agitations, excursions, or, sometimes, jabs) are performed to induce the transfer of the lymph node material into the lumen of the needle helped by either only capillary action or application of suction in addition to the capillary action [16]. These revolutions are likely to be instrumental in pushing the lymph node material into the needle lumen (assisted by suction and capillary action). Whether the number of revolutions made during the procedure affects the diagnostic yield remains unknown. We hypothesized that the use of 20 revolutions would produce a higher diagnostic yield of the procedure. In this study, we explore the effect of the number of revolutions (10 or 20) performed during intrathoracic lymph node sampling with EBUS-TBNA on the diagnostic yield in subjects suspected to have sarcoidosis.

Methods

This was a randomized controlled trial conducted between August 2016 and September 2017 in the bronchoscopy suite of the Postgraduate Institute of Medical Education and Research, Chandigarh, India. The study protocol was approved by the Institute Ethics Committee (NK/2232/study/1116), and a written informed consent was obtained from all subjects. The trial was registered at www.clinicaltrials.gov (NCT02875756).

Patient Selection

We included consecutive subjects with clinical and radiological suspicion of sarcoidosis if they met all the following criteria: (a) age between 18 and 85 years; (b) enlarged hilar and/or mediastinal lymph nodes >10 mm (any axis) on computed tomography (CT) of the chest; and, (c) planned for EBUS-TBNA. Subjects were excluded if any of the following was present: (a) hypoxemia ($\text{SpO}_2 < 92\%$ on $\text{FiO}_2 \geq 0.3$); (b) treatment with systemic glucocorticoids for >2 weeks in the preceding 3 months; (c) diagnosis of sarcoidosis possible with another minimally invasive technique such as skin biopsy or peripheral lymph node sampling; or, (d) failure to provide informed consent.

Randomization

Subjects were randomized 1:1 to undergo EBUS-TBNA with the performance of either 10 (group 1) or 20 revolutions (group 2) inside the lymph node during every pass (Fig. 1). The computer-generated randomization sequence was placed in sealed opaque envelopes that were opened sequentially immediately before the procedure. The subject and the cytologist were blinded to the group assignment.

Study Procedure

Before EBUS-TBNA, the subjects underwent clinical examination and standard laboratory tests including a tuberculin skin test, spirometry, chest radiography, and CT of the chest.

All bronchoscopic procedures were performed in an outpatient setting under monitored conscious sedation by consultants experienced in the procedure or fellows supervised by the consultants. Premedication, topical anesthesia, and sedatives were administered using a standard protocol, as described previously [17, 18]. EBUS-TBNA was performed orally in the supine position using an EBUS bronchoscope (BF-UC180F; Olympus Medical, Japan) and a compatible ultrasound image processor (EU-ME1; Olympus Medical) [19]. Enlarged lymph nodes were identified, and the size of the lymph nodes was measured [20]. The lymph nodes were aspirated using the jabbing method under real-time ultrasound control with a dedicated 22G EBUS-TBNA aspiration needle (Vizishot, NA-201 SX-4022A; Olympus Medical). Continuous suction was applied with a 20-mL Vacloc syringe while the catheter was moved back and forth for either 10 or 20 times according to the allocated study group. ROSE was not available. Two or more lymph node stations were accessed, and at least 2 passes were obtained from each lymph node sampled. Conventional bronchoscopy procedures, including EBB and TBLB, were performed at the discretion of the bronchoscopist [7, 21].

Specimen Preparation

Slides prepared from the EBUS-TBNA aspirates were either air-dried (for Ziehl-Neelsen staining) or immediately fixed in 95% alcohol (for cytological examination). The aspirate was also sent in saline for mycobacterial culture and Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) [22].

Diagnosis of Sarcoidosis

Sarcoidosis was diagnosed on the basis of compatible clinical and radiological presentation, presence of nonnecrotic granulomas in any of the bronchoscopic specimens (EBUS-TBNA, EBB, or TBLB), and exclusion of similar presenting conditions [19, 23]. When granulomas were not demonstrated, a diagnosis of sarcoid-

Fig. 1. CONSORT diagram showing the flow of the participants in the study.

osis was made based on the presence of a consistent clinicoradiological presentation, with no alternate diagnosis made at the 6-month follow-up, and there was either spontaneous regression of the symptoms (and/or lymph nodes) or good response to empiric glucocorticoid therapy [24].

Endpoints

The primary endpoint was the diagnostic yield (sensitivity) of EBUS-TBNA in subjects finally diagnosed to have sarcoidosis. The secondary endpoint was adequacy of the samples. A specimen was termed as diagnostic if it showed epithelioid cell granulomas and as adequate if the aspirate was either diagnostic or showed preponderance of lymphocytes.

Sample Size

The sample size was calculated based on a reported yield of 75% in group 1 [7, 8] and a presumed increase in yield by 10% in group 2 (i.e., 85%). With these assumptions, 270 subjects would be required in each group (confidence level [1- α] 95%, power level [1- β] 80%) to detect this difference. As this sample size was not logistically feasible, a convenience sample of 150 subjects was chosen.

Statistical Analysis

Data are presented as means (standard deviation [SD]) or number (percentage). The commercial statistical package SPSS (version 22.0; IBM Inc., United States) was used for performing all data analysis. The χ^2 test (or Fisher's exact test) or Student *t* test was used to analyze differences between categorical and continuous variables, respectively. A *p* value <0.05 was considered significant.

Results

Of the 171 screened subjects (Fig. 1), 150 were randomized to undergo EBUS-TBNA with either 10 (*n* = 75) or 20 revolutions (*n* = 75). The baseline characteristics were similar between the 2 groups (Table 1). There was no significant difference in the mean size of the lymph nodes sampled. The most common lymph node sampled

Table 1. Baseline characteristics of the study population

	Group 1 (<i>n</i> = 75)	Group 2 (<i>n</i> = 75)	Total (<i>n</i> = 150)	<i>p</i> value
Age, years	45.3±11.9	41.8±10.9	43.5±11.5	0.06
Female gender	37 (49.3)	34 (45.3)	71 (47.3)	0.74
TST negativity (<10 mm)	63 (84.0)	67 (89.3)	130 (86.7)	0.47
Stage				0.74
I	44 (58.7)	41 (54.7)	85 (56.7)	
II	31 (41.3)	34 (45.3)	65 (43.3)	
Size of sampled lymph nodes on EBUS (short axis), mm	15.7±3.4	15.9±2.2	15.8±3.3	0.69
Size of largest lymph node sampled on EBUS (short axis), mm	19.9±4.3	20.7±5.6	20.3±4.9	0.36
Lymph nodes sampled, <i>n</i>	2.8±0.8	2.7±0.7	2.8±0.7	0.37
Passes per node, <i>n</i>	2.1±0.5	2.1±0.5	2.1±0.5	0.60
Stations sampled				
4R	61	68	129	0.16
4L	14	7	21	0.16
7	73	71	144	0.68
10R	3	7	10	0.33
10L	1	2	3	1.00
11R	11	6	17	0.30
11L	49	43	92	0.40
Additional procedures performed				
EBB	70 (93.3)	71 (94.7)	141 (94.0)	1.00
TBLB	62 (82.7)	67 (89.3)	129 (86.0)	0.35

All values are presented as *n* (%) or mean ± SD. EBUS, endobronchial ultrasound; TST, tuberculin skin test.

was the station 7, followed by station 4R and 11L. The number of lymph nodes sampled and the number of passes per lymph node were similar in the 2 groups (Table 1). We performed EBB and TBLB in 141 (70 in group 1 and 71 in group 2) and 129 (62 in group 1 and 67 in group 2) subjects, respectively, and were not different between the 2 groups.

Endpoints

Sarcoidosis was diagnosed in 133 (65 in group 1 and 68 in group 2) subjects. Other diagnoses made on EBUS-TBNA included tuberculosis (*n* = 11), metastatic carcinoma (*n* = 2), lymphoma (*n* = 1), and reactive lymphadenopathy (*n* = 3). Of the 133 subjects with sarcoidosis, granulomas were demonstrated by EBUS-TBNA in 109 (82.0%). There was no difference (*p* = 0.65) in the diagnostic yield of EBUS-TBNA (Table 2) between the 2 groups (group 1 [52/65, 80.0%] vs. group 2 [57/68, 83.8%]). Of the 109 subjects diagnosed on EBUS-TBNA, EBB was performed in 103 and was diagnostic in 30 (29.1%), while TBLB was performed in 97 subjects and was diagnostic in 49 (50.5%). Of the remaining 24 subjects (with a non-diagnostic EBUS-TBNA), 14 had non-

necrotic granulomas demonstrated in EBB or TBLB (2 on EBB, 6 on TBLB, and 6 on both), and the remaining 10 were diagnosed on the basis of the clinicoradiological presentation and follow-up. Overall, EBB was diagnostic in 38 (29.9%) of the 127 subjects with sarcoidosis in whom it was performed. TBLB, when performed, was diagnostic in 61 (52.1%) of the 117 subjects with sarcoidosis.

An adequate aspirate was obtained in 129 of the 133 (97.0%) subjects with sarcoidosis and was not different between the 2 groups (Table 2). The mean (SD) duration of the EBUS-TBNA procedure was 16.9 (4.0) min and was also not significantly different between the groups (16.4 [3.5] and 17.4 [4.4] min in groups 1 and 2, respectively; *p* = 0.17). The specimen was grossly contaminated with blood in 7 (5.3%) subjects and was not significantly different between the 2 groups. Five complications occurred (bleeding at the puncture site in 1, pneumothorax in 2, and hypoxemia in 2 subjects) and were not different between the 2 groups. Pneumothorax was minimal in 1 subject, while the other subject required a single-time aspiration. Pneumothorax was attributed to TBLB in both cases.

Table 2. Study outcomes in subjects with a final diagnosis of sarcoidosis

	Group 1 (<i>n</i> = 65)	Group 2 (<i>n</i> = 68)	Effect size (95% CI)	<i>p</i> value
Primary outcome				
Diagnostic yield	52 (80.0)	57 (83.8)	3.8 (−9.3 to 17.0)	0.65
Secondary outcome				
Adequacy of the specimen	63 (96.9)	66 (97.1)	0.14 (−7.4 to 7.9)	1.00
Other outcomes				
Gross contamination of the aspirate by blood	3 (4.6)	4 (5.9)	1.3 (−7.6 to 10.1)	1.00
Duration of the EBUS procedure, min	16.4±3.5	17.4±4.4	1.0 (−0.4 to 2.4)	0.17
Complications	2 (3.1)	3 (4.4)	1.3 (−6.7 to 9.4)	1.00
Moderate-to-severe bleeding	0	1		
Hypoxemia	1	1		
Pneumothorax	1	1		

All values are presented as *n* (%) or mean ± SD unless otherwise specified. CI, confidence interval.

Table 3. Studies describing technical aspects of the EBUS-guided TBNA procedure in subjects with sarcoidosis

First author [ref.], year	Study design	<i>n</i>	Characteristics explored	Major findings
Sun [11], 2015	Prospective, observational	120	Number of lymph nodes and passes	Yield increased up to 3 lymph nodes sampled and up to 5 needle passes
Muthu [8], 2016	Randomized	150	21G vs. 22G EBUS-TBNA needle	No difference in the yield with either needle
Biswas [12], 2017	Prospective, observational	11	19G cTBNA needle through EBUS vs. 22G EBUS-TBNA needle	19G needle yielded tissue with a better preserved cellular architecture and a higher yield of definite, well-formed granuloma
Madan [9], 2017	Randomized	80	ROSE vs. no ROSE	No difference in the yield between the 2 groups
Oki [13], 2018	Prospective, observational	109	Number of lymph nodes and passes	Cumulative yield increased for up to 4 passes; not different whether 1 or 2 lymph nodes were sampled

cTBNA, conventional TBNA; EBUS, endobronchial ultrasound; ROSE, rapid on-site evaluation.

Discussion

The results of this study suggest that there is no difference in the diagnostic yield or the adequacy of the specimen obtained using EBUS-TBNA with either 10 or 20 revolutions of the needle within the node in subjects with sarcoidosis. In the current study, we enrolled subjects with suspected sarcoidosis to ensure the uniformity of the study population. Further, the yield of EBUS-TBNA in sarcoidosis is intermediate (between other diseases with enlarged mediastinal lymph nodes such as lung cancer and lymphoma); thus, there was a higher chance of a

technical aspect of the procedure affecting the diagnostic yield [25].

We had hypothesized that a higher number of revolutions would increase the likelihood of the lymph node material to get aspirated into the needle lumen. However, the final yield did not differ significantly between the 2 groups. Certain points deserve special mention. First, we did not look at the yield for every pass made in either group. An average of 3 lymph nodes were sample per subject and an average of 2 passes were made per lymph node, totaling to an average of 6 passes per subject. With 6 passes it is possible that the cumulative yield tended to

plateau equally in both groups. Thus, the effect of the number of revolutions on the yield during a single pass might have canceled out over 6 passes. Second, the time spent by the needle inside the lymph node while making a pass, mentioned as typically <6 s in a previous article, was not recorded [26]. It is difficult to predict what role the time the needle resides within the lymph node played in affecting the yield in either group. Third, in our experience, we had observed that with an increasing number of revolutions made inside the node, there is a higher chance of inadvertently hitting an intranodal vessel, resulting in gross blood contamination of the aspirate. Due to this blood contamination, there is a chance of a reduced yield, as granulomas may get entangled in a blood clot. Blood clot histologic analysis, as described in a previous study, is not performed routinely at our center [27]. However, gross blood contamination occurred equally in both groups, thus falsifying our general observation.

The duration of the EBUS procedure was not different between the 2 groups. With a smaller number of revolutions performed inside the node, the 10-revolutions group would potentially have allowed shorter procedures; however, this did not occur. It is because the movement of the needle inside the node forms just a small fraction of the overall EBUS-TBNA procedure. Further, we used a single EBUS-TBNA needle for each subject. Thus, time was spent with every pass in pushing the sample out of the needle for processing onto glass slides and saline solution before the needle was made ready for the next pass. Another important point that needs discussion is that ROSE was also not available. It is possible that the use of ROSE could have helped us reduce the number of passes and the duration of the procedure. Further, ROSE can help avoid additional procedures such as EBB and TBLB if granulomas with significant necrosis can be identified, as this finding would suggest a diagnosis other than sarcoidosis, such as tuberculosis, in our setting. However, in case of finding nonnecrotic granulomas, it may still not be possible to avoid these procedures. In a tuberculosis-endemic setting, the results of EBB and TBLB can further help in differentiating sarcoidosis from tuberculosis. If nonnecrotic granulomas are identified in TBLB in cases of a normal lung (on high-resolution CT), the diagnosis is likely to be sarcoidosis [28]. On the other hand, sometimes, necrotic granulomas can be identified in TBLB (due to the larger piece of tissue obtained with lung biopsies compared to a lymph node aspirate), which helps make a diagnosis of tuberculosis.

A few studies have analyzed various technical aspects of the EBUS-TBNA procedure in subjects with sarcoid-

osis (Table 3) [8, 9, 11–13]. Two prospective observational studies have shown that the diagnostic yield increases for up to 4 or 5 total passes made [11, 13]. In the first study, the yield was also found to increase with the number of lymph nodes sampled and plateaued at 3 lymph nodes [11]. In the other study, there was no difference in the yield with sampling of either 1 or 2 lymph nodes [13]. Other studies in subjects with sarcoidosis have shown no difference in the yield with either the 21G or 22G needle or with the use of ROSE [8, 9]. A small study of 11 subjects showed that the 19G conventional TBNA needle, when used with the EBUS scope, yielded tissue with better preservation of cellular architecture than that obtained with the 22G needle [12]. In studies performed in general populations of subjects with mediastinal lymphadenopathy (not specifically sarcoidosis) undergoing EBUS-TBNA, it has been demonstrated that the use of either suction or the stylet provided with the EBUS-TBNA needle does not affect the diagnostic yield [16, 29]. The use of a novel flexible 19G needle has also been investigated in preliminary studies [30, 31]. Before the present study, there was no report on the effect of the number of revolutions performed inside the lymph node on the diagnostic yield. The recent American College of Chest Physicians guidelines on the technical aspects of EBUS-TBNA mention that 5–15 agitations of the needle are typically performed while sampling a lymph node [15].

Finally, our study has certain limitations. It is a single-center study with a small sample size. We did not assess the yield for every pass in the 2 groups. ROSE and histological analysis of cell block specimens were not performed. However, this is the first study addressing this procedural aspect of EBUS-TBNA in any patient population. As the study included only subjects with sarcoidosis, the results may not be generalizable to patients with lung cancer or other causes of mediastinal lymph node enlargement.

In conclusion, there is no difference in the yield of EBUS-TBNA performed with either 10 or 20 revolutions of the needle inside the lymph node in subjects with sarcoidosis.

Disclosure Statement

All authors declare no conflicts of interest and financial disclosures.

Author Contributions

S.D.: involved in patient management, statistical analysis, drafting and revising the manuscript. I.S.S., N.G., A.B., K.T.P., and

A.N.A.: involved in patient management, revising the manuscript. B.R.: involved in patient management, data collection, and revising the manuscript. R.A.: conceived the idea, involved in patient management, revising the manuscript.

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