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A randomized comparison of sample adequacy and diagnostic yield of various suction pressures in EBUS-TBNA

Abstract

Introduction: The evidence for using vacuum suction during EBUS is sparse and the optimal suction pressure for obtaining adequate samples has not yet been determined. Our aim was to assess the influence of suction on the adequacy and diagnostic yield of EBUS-TBNA.

Material and methods: This single-center, prospective, randomized, non-inferiority trial assessed whether no-suction and 10 mL suction are inferior to 20 mL suction for adequacy and diagnostic yield of EBUS-TBNA aspirates.

Results: Three hundred twenty three lymph nodes were sampled using EBUS-TBNA. Baseline characteristics of lymph nodes were comparable in the three suction groups. The overall adequacy of EBUS-TBNA aspirates in the no-suction, 10 mL, and 20 mL suction was 90%, 83.49%, and 77.88%, respectively. The differences in adequacy were 12.1% (95% CI: 3.9–20.3) and 5.6% (95% CI: –3.3–14.5) for no-suction *vs* 20 mL, and 10 mL *vs* 20 mL suction, respectively. No-suction and 10 mL were not inferior to 20 mL suction in terms of sample adequacy. At a superiority margin of 3.92%, no-suction was superior to 20 mL suction in terms of sample adequacy ($p < 0.05$). The overall diagnostic yield was comparable (63.6%, 52.3%, and 57.7% in 0, 10 mL, and 20 mL, respectively; p-value was not significant). The proportion of aspirates which were predominantly bloody was similar (no-suction — 10.9%, 10 mL — 13.8%, 20 mL — 15.4%; $p = 0.62$).

Conclusions: EBUS-TBNA with or without the application of vacuum suction does not influence specimen adequacy and diagnostic yield.

Key words: EBUS-TBNA, diagnostic yield, sample adequacy, suction

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Introduction

Assessment and sampling of enlarged mediastinal lymph nodes has traditionally been done using flexible bronchoscopy-guided transbronchial needle aspiration (TBNA), CT-guided biopsy, or mediastinoscopy. Over the past decade, endobronchial ultrasound-guided TBNA (EBUS-TBNA) has become an essential investigation in accessing mediastinal structures providing sample adequacy between 85 to 93% [1, 2] and a diagnostic yield ranging from 37 to 90 % [3, 4].

Several factors are known to influence the yield of EBUS-TBNA, including: the needle size [5], number of passes performed [6], and nodal size [4]. In clinical practice, EBUS-TBNA is commonly performed by applying vacuum suction, although evidence regarding its utility is inconsistent [7, 8]. Consequently, a recent technical Working Group report also suggested that EBUS-TBNA may be performed with or without the application of suction [9]. The likely benefit obtained by using suction should be weighed against the increased possibility of bloody aspirates. Very few studies have performed a systematic comparison of different suction pressures in EBUS, and most of them have focused primarily on lymphadenopathy due to malignant etiology. However, benign disorders such as tuberculosis

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and sarcoidosis form a significant proportion of referrals for EBUS in several settings [7, 10].

Given the fact that vacuum suction is considered to be an essential step in the EBUS procedure, we aimed to determine the optimum suction pressure for both malignant and benign mediastinal lesions by comparing the sample adequacy and diagnostic yield of EBUS-TBNA aspirates using three different suction pressures (no-suction, 10 mL suction, and 20 mL suction).

Material and methods

This was a prospective, randomized, single-blinded, non-inferiority study performed at an academic tertiary level hospital in North India. Adult patients referred for EBUS for undiagnosed hilar or mediastinal lymphadenopathy and having a lymph node size more than 0.5 cm in the short axis as seen on the EBUS ultrasound image, were recruited. Patients with cardiovascular comorbidities such as ischemic heart disease or uncontrolled hypertension, and subjects with deranged coagulation profile were excluded. Necessary ethical approval was obtained from the local Institution Ethics Committee vide Ref No. IECPG-272/07.09.2017 dated 27.10.2017. The trial was registered in the clinical trials registry of India (CTRI 2017/10/010202) and was conducted according to the CONSORT recommendations [11].

Study technique

After obtaining informed written consent, EBUS was performed with the help of intravenous sedation and analgesia (midazolam and fentanyl). Two percent lignocaine, using the 'spray as you go' technique, was used for topical anesthesia. The Olympus BF-UC-180F EBUS scope (Olympus. Medical Systems, Tokyo, Japan) equipped with an ultrasound transducer at the tip and dedicated ultrasound image processor (Olympus EU-ME1) (Olympus. Medical Systems, Tokyo, Japan) was used for all procedures. Lymph nodes greater than 0.5 cm in the short axis on the EBUS ultrasound image were sampled. For study purposes, only one lymph node per patient was sampled using a 21G needle (Single Use Aspiration Needle, ViziShot, Olympus. Medical Systems, Tokyo, Japan). EBUS-TBNA was performed by one of 5 operators who had experience performing more than 100 procedures each.

Additional lymph nodes, if sampled, were not included for analysis but were used for clinical decision-making. The lymph node of interest was randomly allocated into either of the three suction pressures (no-suction, 10 mL, or 20 mL) using a random number sequence generated by a staff member who was not an active participant in the study. Three needle punctures were performed into each lymph node with the randomly allocated suction pressure. Material obtained with these three passes was smeared onto a slide to assess for adequacy and diagnostic yield. The fixed smears were stained using Papanicolaou stain and evaluated under a microscope by the cytopathologist for sample adequacy [12]. Cell-block and liquid-based cytology were not done routinely for all patients as a protocol in our pathology department. Rapid On-site Evaluation (ROSE) was not used to guide the sampling of the index lymph node. The final diagnosis was made by a dedicated pathologist who was unaware of the amount of suction applied.

The primary outcome measured was the comparison of specimen adequacy between groups, while the secondary outcome measured was diagnostic yield. An adequate sample was defined as showing one of the following: presence of lymphocytes, carbon-laden macrophages, necrosis, and/or definite diagnostic material (i.e. malignant cells, acid-fast bacilli, necrotizing or non-necrotizing granuloma) [12]. The diagnostic sample was defined as the proportion of procedures where specimens demonstrated positivity for tuberculosis (TB) (i.e. presence of acid-fast bacilli or necrotizing granulomas), non-necrotizing granulomas, or malignant cells.

Statistical analysis

Sample size was calculated for a three-group parallel non-inferiority trial keeping 20 mL suction as the control pressure and 10mL and no-suction as the test groups to compare EBUS-TBNA sample adequacy rates based on the assumption that there would be 80% adequacy in each of the suction pressure groups with a 15% non-inferiority margin, 95% confidence level, and 80% power [13]. Based on the above, the number of patients required in each group was 100. Hence, the goal was to recruit a minimum of 300 patients. Data were managed on an Excel spread sheet. For comparison of baseline characteristics, continuous variables following normal distribution were monitored by the independent t-test (for two groups) and one-way ANOVA (for more than two independent groups) followed by a post-hoc comparison using the Bonferroni method of p-value correction. The association of categorical variables was assessed by the Chi-square test/Fisher

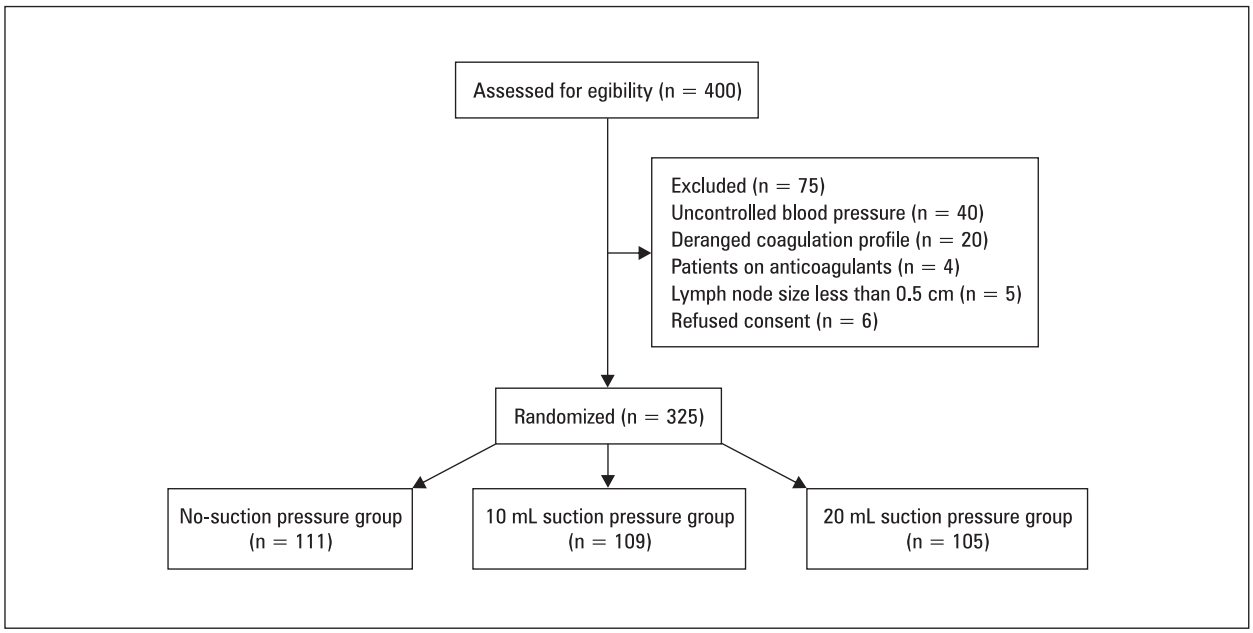

Figure 1. Process of subject recruitment

exact test as appropriate. The difference between various suction pressures in terms of adequacy and diagnostic yield was assessed. All analysis was performed using STATA version 14 (TX: StataCorp LP) and a p-value < 0.05 was considered to be statistically significant.

Results

The study was conducted between September 2017 and February 2019 at a tertiary care teaching hospital in India. The recruitment and evaluation process of the study is depicted in Figure 1. After randomization, the procedure could not be completed in two subjects; hence, these were not included in the final analysis of adequacy and diagnostic yield. The study included 325 patients (60% males) with a mean (standard deviation) age of 46.9 (15.8) years. The baseline characteristics of the study group are depicted in Table 1. Of all the subjects, 111 (34.2%) were randomized in the no-suction group, 109 (33.5%) in the 10 mL suction group, and 105 (32.3 %) in the 20 mL suction group. Table 2 depicts the characteristics of patients in each of the three suction pressure groups.

Table 1. Baseline characteristics of study patients

Characteristic	Value
Total number of patients	325
Gender	
Male	195 (60)
Female	130 (40)
Age [years]	46.9 ± 15.8
Indication of EBUS	
Diagnostic	306
Staging	18
Both	1
Total number of lymph nodes sampled	323
Lymph node size [mm]	13.8 ± 6.1
Lymph node stations sampled	
Right paratracheal (4R)	133 (41.2)
Subcarinal (7)	110 (34)
Left interlobar (11L)	28 (8.7)
Left paratracheal (4L)	21 (6.5)
Right interlobar (11R)	19 (5.9)
Right hilar (10R)	10 (3.1)
Left upper paratracheal (2L)	1 (0.3)
Ill-defined mass	1 (0.3)

Data presented as number (%) or mean ± SD

Lymph node characteristics

The lymph node characteristics including size (short axis), echogenicity, calcification, coagulation necrosis, central hilar structure, presence of intranodal vessels, consistency, and margins were noted in all three groups (Table 3). No difference was observed between the groups with respect to any of the above-mentioned nodal characteristics.

Table 2. Characteristics of all patients in the three suction groups

Variable	No-suction	10 mL suction	20 mL suction	P-value
Gender				
Male	74 (66.7)	65 (59.6)	56 (53.3)	0.14
Female	37 (33.3)	44 (40.4)	49 (46.7)	
Age [years]	46.4 (15.2)	46.6 (17.0)	47.7 (15.2)	0.81
Size [mm]	13.8 (6.3)	14.1 (6)	13.4 (6.2)	0.68
Lymph node station sampled				
Right paratracheal	48 (43.7)	37 (33.9)	48 (46.2)	
Subcarinal	37 (33.6)	44 (40.4)	29 (27.9)	
Others	25 (22.7)	28 (25.7)	27 (25.9)	

Data presented as number (%)

Table 3. Characteristics of lymph nodes in the three suction groups

Characteristic	No-suction (n = 110)	10 mL suction (n = 109)	20 mL suction (n = 104)	P-value
Echogenicity				
Homogeneous	77 (70)	76 (69.7)	76 (73.1)	0.84
Heterogeneous	33 (30)	33 (30.3)	28 (26.9)	
Calcification				
Present	7 (6.4)	3 (2.8)	3 (2.9)	0.41
Absent	103 (93.6)	106 (97.2)	101 (97.1)	
Coagulation necrosis				
Present	15 (13.6)	12 (11)	10 (9.6)	0.64
Absent	95 (86.4)	97 (89)	94 (90.4)	
Central hilar structure				
Present	7 (6.4)	7 (6.4)	4 (3.8)	0.69
Absent	103 (93.6)	102 (93.6)	100 (96.2)	
Intranodal vessels				
Present	6 (5.5)	8 (7.3)	7 (6.7)	0.85
Absent	104 (94.5)	101 (92.7)	97 (93.3)	
Margins				
Discrete	107 (97.3)	107 (98.2)	100 (96.2)	0.65
Ill defined	3 (2.7)	2 (1.8)	4 (3.8)	
Consistency				
Firm	105 (95.5)	106 (97.3)	101 (97.1)	0.59
Soft	1 (0.9)	2 (1.8)	2 (1.9)	
Hard	4 (3.6)	1 (0.9)	1 (1)	
Node size [mm]	13.8 ± 6.3	14.1 ± 6	13.4 ± 6.2	0.68

All values expressed as number (%) or mean ± SD

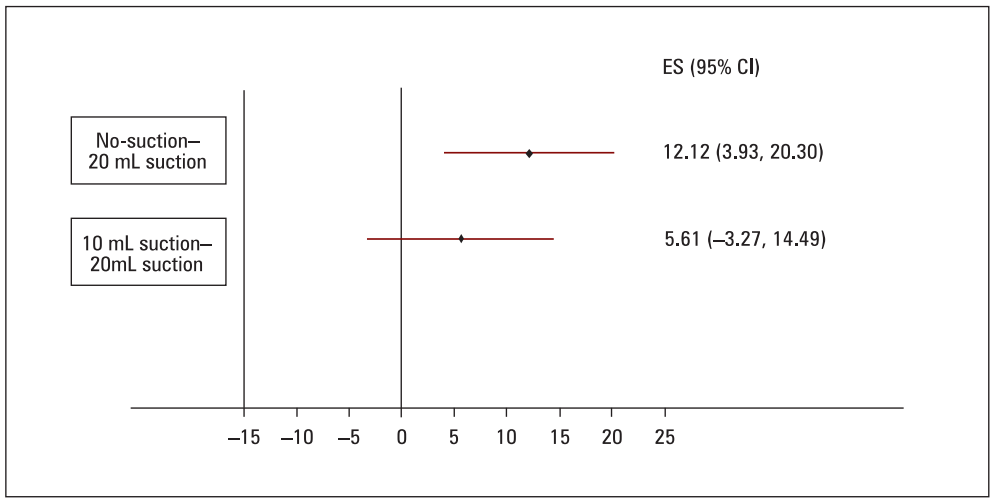

Figure 2. Difference in sample adequacy between "no-suction" and 20 mL suction, and between 10 mL and 20 mL suction pressure

Table 4. Specimen adequacy in the three suction pressure groups

Specimen adequacy	No-suction (n = 81)	10 mL suction (n = 68)	20 mL suction (n = 70)	P-value
Sarcoidosis (n = 100)	37/39 (94.9) [82.7–99.4]	28/30 (93.3) [77.9–99.2]	27/31 (87.1) [70.2–96.4]	0.53
Tuberculosis (n = 78)	23/25 (92) [73.9–99]	23/27 (85.2) [66.3–95.8]	19/26 (73.1) [52.2–88.4]	0.18
Ca-Lung (n = 41)	17/17 (100) [80.5–100]	9/11 (81.8) [48.2–97.7]	11/13 (84.6) [54.6–98.1]	0.16

Data presented as number (%) and [95% confidence interval]

Comparison of sample adequacy of EBUS-TBNA aspirates with either of the three suction pressures in all patients

The overall adequacy of EBUS-TBNA aspirates in the no-suction, 10 mL suction, and 20 mL suction groups was 90%, 83.49%, and 77.88%, respectively. The difference between the no-suction group and 20 mL negative suction group was 12.12% (95% CI: 3.93–20.3). The difference in the adequacy between 10 mL suction and 20 mL negative suction was 5.61 % (95% CI: –3.27–14.49). No-suction and 10 mL suction were not inferior to 20 mL suction in terms of adequacy of EBUS-TBNA aspirates (Figure 2). It was observed that no-suction was not inferior to 20 mL suction for sample adequacy, with a difference of 12.12% (95% CI: 3.93–20.3). Thus, the 95% confidence interval of the effect lies not only above our non-inferiority margin, but also lies entirely above 0. It was also seen that, at a superiority margin of 3.92%, no-suction pressure was superior to 20 mL suction pressure in terms of sample adequacy ($p < 0.05$) [13].

The three common diseases which comprised almost 70% of our cases were sarcoidosis, tuberculosis, and bronchogenic carcinoma (excluding procedures for lung cancer staging). A subgroup analysis comparing the adequacy of EBUS-TBNA in each of the three suction pressures in these diseases was performed and was found to be similar (Table 4).

Comparison of diagnostic yield of EBUS-TBNA aspirates between the three suction pressures

The overall diagnostic yield of EBUS-TBNA aspirates in the no-suction, 10 mL suction, and 20 mL suction groups was 63.6%, 52.3%, and 57.7%, respectively. The difference in the diagnostic yield between the three suction pressures was not statistically significant when computed for the entire patient group, or within each of the above disease categories (Table 5).

Table 5. Diagnostic yield in the three suction pressure groups

Diagnostic yield	No-suction (n = 191)	10 mL suction (n = 177)	20 mL suction (n = 174)	P-value
Overall (n = 323)	70/110 (63.6) [53.9–72.6]	57/109 (52.3) [42.5–61.9]	60/104 (57.7) [47.6–67.3]	0.24
Sarcoidosis (n = 100)	29/39 (74.4) [57.9–86.9]	19/30 (63.3) [43.9–80.1]	21/31 (67.7) [48.6–83.3]	0.61
Tuberculosis (n = 78)	19/25 (76) [54.9–90.6]	17/27 (62.9) [42.4–80.6]	15/26 (57.7) [36.9–76.6]	0.37
Ca-Lung (n = 41)	13/17 (76.5) [50.1–93.2]	8/11 (72.7) [39–93.9]	10/13 (76.9) [46.2–94.9]	0.9

Data presented as number (%) and (95% CI)

Influence of lymph node characteristics on EBUS sample adequacy

In all the three suction groups, there was no association between sample adequacy and lymph node characteristics. Similarly, the mean size (short axis) of the lymph node did not differ between the adequate and inadequate samples in the no-suction and 10 mL suction groups. However, in the 20 mL suction subgroup, the mean node size in the adequate samples was 14.1 mm, which was significantly higher than the node size in inadequate samples (10.8 mm).

Influence of lymph node characteristics on the diagnostic yield

Heterogeneous lymph nodes had a better diagnostic yield in the 20 mL suction group. Similarly, in the no-suction and 20 mL suction group, the mean size of the lymph nodes from which diagnostic samples were obtained was significantly higher than non-diagnostic nodes. The remaining lymph node characteristics did not influence the diagnostic yield in any of the three suction groups.

Complications

The proportion of EBUS-TBNA bloody aspirates was similar in the three suction groups (no-suction: 10.9%, 10 mL – 13.8%, 20 mL – 15.4%; p = 0.62)

Discussion

The results of the present study indicate that EBUS-TBNA performed with no-suction or 10 mL suction is not inferior to 20 mL suction pressure for sample adequacy. The amount of suction did not influence the diagnostic yield. Traditionally, most operators have used negative vacuum suction pressures in the hope of acquiring good cellular material for cytology. However, this is based mostly on individual experiences and extrapolation from the technique of conventional TBNA where negative suction is advocated [14].

Our results show that overall specimen adequacy of EBUS-TBNA aspirates using no-suction was higher than that obtained by 10 mL suction and 20 mL suction (90%, 83.49%, and 77.88% respectively). This indicates that EBUS-TBNA without suction provides the highest proportion of adequate samples for cytopathological analysis. As per our results, both no-suction and 10 mL suction were not inferior to 20 mL suction pressure in terms of sample adequacy. Furthermore, we found that the no-suction technique was actually superior to 20 mL suction with a superiority margin of 3.92%. Also, within the subgroups of sarcoidosis, tuberculosis, and lung cancer, adequacy of EBUS-TBNA aspirates obtained by each of the three suction pressures was similar.

Comparisons between different suction pressures for obtaining samples while performing EBUS have been sparsely reported. The study by Casal *et al.* [7] compared the concordance between no-suction and 10 mL suction during EBUS-TBNA and found no difference between the adequacy (88% *vs* 88%) or quality of samples. Their study design differed from ours in that they applied each of the two suction pressures on the same lymph node. Similarly, two other authors have also reported similar specimen adequacy using no-suction or 20 mL suction [1, 2]. The adequacy obtained in these studies was higher than that obtained in our study. However, in one of those studies, the authors performed four needle punctures per node and applied both suction pressures in the same node for two passes each. It is possible that puncturing the node using one suction pressure could have altered the nodal architecture and influenced the yield of the

suction pressure applied subsequently. Keeping these limitations in view, this study was designed to only obtain a sample from each lymph node with a randomly assigned suction pressure.

On the other hand, few studies have reported better yields with higher suction pressure. Boonsarngsuk *et al*. [8] compared 0 mL, 20 mL, and 40 mL suction pressure in EBUS-TBNA and found no difference in the adequacy and diagnostic yield between 20 mL and 40 mL suction pressure. However, both of these were superior to the results obtained by zero suction. Although this was the only study to compare three different suction pressures, it enrolled only 66 patients in whom one pass was performed using each of the three pressures. Thus, the possibility of the first-pass effect may have influenced the results. Furthermore, it must be kept in mind that the Vaclok syringe provided with the EBUS scope has a maximum capacity of 20 mL suction. The study mentioned above used a customized syringe to apply 40 mL suction. This may have compromised the uniformity of study methodology and adds to the cost and logistic difficulties in a real-world setting.

The overall diagnostic yield of EBUS-TBNA in our study was similar in each of the suction groups (no-suction: 63.6%, 10 mL: 52.3%, and 20 mL: 57.7%; p = not significant). Subgroup analysis revealed that the diagnostic yield was highest in lung cancer in all three of the suction categories compared to TB and sarcoidosis, although no statistical difference was observed. The overall diagnostic yield was relatively low compared to several previous reports, but comparable to that reported in the large AQuIRE registry [4]. There are several reasons that may explain this finding. Firstly, we calculated the yield based on the cytological results of the first three passes with either of the three suction pressures. The results of additional passes, if obtained, were not included in the final analysis. Secondly, only the findings of cytological smears were taken into account while calculating the diagnostic yield. The results from other investigations such as clot core biopsy, cell blocks, and GeneXpert were not considered since they are not done at our center as routine protocol. It has been reported that GeneXpert may provide additive value in EBUS-TBNA for the diagnosis of tuberculosis [15].

However, the diagnostic yield of our study was better than previous studies which had the same hypothesis. Casal *et al*. [7] found a diagnostic yield of 36% and 34% in the 10 mL suction and no-suction groups, respectively. In malignant disorders, the yield was even lower (28% and 26%, respectively). Lin *et al*. [2] compared use of suction *vs* no-suction and stylet *vs* no stylet and reported a diagnostic yield of 32.2% (suction–stylet), 31.8% (suction–no stylet), and 31% (stylet–no-suction). Various registries on the diagnostic yield of EBUS-TBNA suggest a wide variation, possibly due to the lack of a stringent and uniform definition of this pathological outcome [4]. In fact, some authors have loosely defined diagnostic yield simply as "the presence of lymphocytes or any specific diagnosis" [4]. In addition, most studies on EBUS emerge from Western countries, where malignancy constitutes a disproportionately high percentage of all procedures. In contrast, the majority of our subjects had a benign disease. This may be an important determinant of sample adequacy or diagnostic yield. The AQuIRE Bronchoscopy Registry (2011) reports unadjusted diagnostic yields of 37% to 54% for different hospitals [4]. A recent Indian study reported a diagnostic yield of 63% among 1,582 patients, with an average of two nodes being sampled [16]. It is known that several factors affect the diagnostic yield of EBUS such as nodal size, number of needle punctures per node, nature of sedation or anesthesia, and size of the needle used [3, 5, 6, 17]. On the other hand, diagnostic yield as low as 27% has also been reported, probably reflecting a real-world medical scenario wherein negative results are high in the absence of a robust and easily available diagnostic gold standard [18]. Similarly, the station of the mediastinal lymph node sampled also has a bearing on the diagnostic yield. A recent study found a positive association between sampling of subcarinal lymph nodes and yield of endosonographic biopsy [19]. This is probably due to ease of sampling this station of lymph nodes. In our study, no association was detected between the mediastinal stations sampled and the diagnostic yield in the three groups. Recently, it has been postulated that ultrasonographic characteristics of lymph nodes influence the adequacy and diagnostic yield of EBUS aspirates [9, 20]. In a retrospective analysis, it was observed that the presence of well-defined margins, central hilar structure, and nodal conglomeration were independent predictors of benign etiology [21]. In our study, all lymph node characteristics were comparable in the three suction groups, except for the fact that nodes yielding adequate samples were larger, and diagnostic yield was better in the heterogeneous nodes in the 20 mL suction group. Similarly, in the no-suction group, nodes that were diagnostic were larger than non-diagnostic

nodes. None of the other nodal characteristics influenced the adequacy or diagnostic yield between the three suction pressure groups.

Bleeding, albeit mild, is one of the most common complications of EBUS-TBNA, followed by other less common events such as arrhythmias, hypotension, and respiratory failure [22]. One of the hypotheses of the current study was that the use of negative suction might lead to bloody aspirates, thereby becoming inadequate and non-diagnostic specimens. This was proven correct because 15.4% of aspirates obtained by 20 mL suction were predominantly bloody, compared to 10.9% and 13.8% using no-suction and 10 mL suction, respectively (this difference was not statistically significant). Similarly, previous studies that analyzed the proportion of bloody samples obtained with and without suction have not found any differences [7]. On the other hand, when using endoscopic ultrasound-guided fine needle aspiration (EUS-FNA), Wallace *et al.* [23] found that the odds of obtaining a bloody aspirate were 4.7 times higher when suction was used compared to without suction. We believe that similar inferences may be drawn for EBUS-TBNA, a procedure that technically resembles EUS.

To our knowledge, this randomized trial is the largest to date that assesses the utility of negative suction during EBUS-TBNA. The fact that we used only one of the three suction pressures per node helped to negate the potential bias likely due to the "first-pass effect". This, along with the "blinding" of the cytopathologist, helped control for the confounding effects of various lymph node characteristics on outcome parameters. Also, the present study had a mix of patients with mediastinal lymphadenopathy due to both benign and malignant diseases, more closely reflecting a real-life clinical scenario and thus making the results more generalizable.

There are some limitations to this study. Firstly, we did not routinely use cell-block or tissue core for the processing of samples. Secondly, GeneXpert and liquid cultures for TB were not analyzed separately for aspirates obtained with each of the three suction pressures and were not used for calculating the study outcomes. Thirdly, the procedures were performed by different operators with varying levels of experience in EBUS, although this possibly makes our results more generalizable. Lastly, EBUS was performed by 5 different operators, which could have influenced the diagnostic yield of the procedure. However, each of the operators had experience (at least 100 independent procedures); hence, it is reasonable to assume that inter-operator variability was unlikely to impact the diagnostic yield of the EBUS procedure. Despite these shortcomings, we feel that this study adds useful information to the technique of EBUS-TBNA and has potential practice-changing implications.

Conclusion

The results of our prospective randomized trial show that EBUS-TBNA performed with or without the application of negative suction does not influence the adequacy and diagnostic yield of the aspirates.

Conflict of interest

None declared.

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