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A randomized trial of narrow band imaging for performing airway mucosal biopsy in pulmonary sarcoidosis (NABS)

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Abstract. *Background:* Data suggest that narrow band imaging (NBI) highlights airway mucosal nodules better than white light bronchoscopy (WLB) in sarcoidosis. No randomized trial has compared the diagnostic yield of endobronchial biopsy (EBB) performed using NBI versus WLB. *Methods:* We performed an investigator-initiated single-center, parallel-arm, randomized trial. Consecutive subjects ≥18 years of age with clinico-radiologic presentation consistent with sarcoidosis were randomised 1:1 to undergo EBB using NBI plus WLB (intervention) or WLB (control). *Outcomes:* The primary outcome was the diagnostic yield of EBB defined by the finding of granulomas on pathologic examination in subjects with a final diagnosis of sarcoidosis. The secondary outcomes included procedure duration and complications. *Results:* We included 150 (mean age, 43.1 years; 53.3% men) subjects; 75 each were assigned to either study group. Sarcoidosis was diagnosed in 126/150 subjects (66 and 60 in the NBI plus WLB and WLB groups, respectively). There was no difference (p=0.53) in the diagnostic yield of EBB between the NBI plus WLB (25/66, 37.9%) and the WLB (26/60, 43.3%) groups. Transbronchial lung biopsy and endobronchial ultrasound-guided transbronchial needle aspiration yielded granulomas in 69 of 115 (60%) and 68 of 98 (69.4%) subjects, who underwent these additional procedures, respectively. In 11 of the 14 (78.6%) cases, where WLB demonstrated airway nodules, NBI enhanced visualization. Moreover, it identified nodules in five additional cases. There were no between-group differences in the procedure duration or complications. *Conclusions:* The use of NBI did not improve the yield of EBB in patients with sarcoidosis. Additional research is warranted. (Clinicaltrials.gov: NCT05311150)

Key words: sarcoidosis, narrow band imaging, bronchoscopy, lung biopsy, diffuse lung disease

Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown cause (1). A consistent clinical and radiologic presentation, detection of non-necrotizing granulomatous inflammation in tissue samples, and the exclusion of other causes of granulomatous disease are key elements for diagnosis (2). In the absence of a more accessible site, thoracic lymph nodes and the lungs are the most commonly sampled organs for diagnosis. Bronchoscopic techniques such as endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA), endobronchial biopsy (EBB), and transbronchial lung biopsy (TBLB) are used to obtain tissue from the thoracic lymph nodes, bronchial mucosa, and the lung parenchyma, respectively (3). Of these, EBUS-TBNA is the most sensitive and the safest procedure with an average diagnostic yield of 70-80% (4).

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When EBB and TBLB are also performed, the cumulative yield of the three techniques is above 90% (5). TBLB alone adds about 10% to the combined yield but is associated with a risk of pneumothorax and lung hemorrhage (6, 7). If the combined yield of EBUS-TBNA and EBB can be increased, it would help avoid TBLB, making bronchoscopic procedures safer for diagnosing sarcoidosis. Narrow-band imaging (NBI) is a novel endoscopic mode of optical image enhancement that emphasizes the contrast of the mucosal and submucosal blood vessels and highlights the finer details of the airway mucosa (8). Recently, an exploratory study suggested that NBI may allow the identification of additional abnormalities not recognized on white light bronchoscopy (WLB) in patients with sarcoidosis (9). In this study, we aimed to examine the diagnostic sensitivity of EBB performed using NBI or WLB in patients with sarcoidosis. We hypothesized that adding NBI to WLB would significantly increase the yield of bronchial mucosal biopsy by allowing better site selection for biopsy.

Materials and Methods

We performed an investigator-initiated, single-center, parallel-arm, randomized trial between April 2022 and December 2023 in the interventional pulmonology suite of our Institute. The study protocol was approved by the Institute Ethics Committee (INT/IEC/2021/SPL-1817). All study subjects provided written informed consent. The trial was registered at www.clinicaltrials.gov (NCT05311150).

Subject selection

We included consecutive subjects if they satisfied the following criteria: (a) age ≥18 years; and, (b) clinical presentation and radiologic findings suggesting sarcoidosis. Subjects were excluded if any of the following was present: (a) unfit for bronchoscopic sampling due to hypotension, marked hypoxemia, or uncorrected coagulopathy; (b) pregnancy; (c) treatment with systemic glucocorticoids ≥3 weeks in the past three months; (d) tissue specimen could be obtained using a less invasive method, such as skin biopsy or peripheral lymph node aspiration; or, (e) failure to provide informed consent.

Randomization

We randomly assigned subjects 1:1 to undergo EBB either using NBI plus WLB or WLB alone. The randomization sequence was computer-generated, in variable block sizes of 4 and 6. The study group was assigned before bronchoscopy by opening consecutively numbered, opaque, sealed envelopes that contained the allocations.

Study procedures

After clinical review and physical examination, subjects underwent laboratory tests including tuberculin skin test (TST), spirometry, chest radiography, and thin-section chest computed tomography (CT). We assigned a CT stage to the disease based on the presence of thoracic lymph node enlargement (LNE) alone (stage I), thoracic LNE and lung abnormalities (stage II), lung abnormalities only (stage III), and fibrotic lung abnormalities (stage IV). Skilled operators (consultants or pulmonary fellows) performed all the bronchoscopic procedures. Conscious sedation (with intravenous midazolam and fentanyl) and topical anesthesia were used during the bronchoscopy, as described previously (10, 11). In the WLB group, we examined the airways using WLB. In the NBI group, first, a WLB examination was performed, followed by an examination using the NBI mode. We noted the presence of endobronchial nodules or 'granularity' by each mode (plaques were considered part of granularity or nodularity). While using the NBI mode, we noted whether the nodules were better highlighted compared to the visualization under the WLB mode. We recorded the vascularity of the nodules (hypovascular, normovascular, or hypervascular). Endobronchial biopsies were then performed in either study group under direct visualization using the NBI mode or WLB per randomization. The flexible video-bronchoscope (BF-1T 180, Olympus Medical, Japan) and the fenestrated alligator forceps [FB15C; Olympus Medical, Japan]) were used to perform the EBB in both groups. The bronchial mucosa was sampled from sites deemed abnormal by the operator under direct visualization with the respective mode. In those with normal-looking airways, EBB was performed from the right secondary carina between the upper lobe bronchus and the bronchus intermedius, and the bifurcation between the middle

lobe and the lower lobe bronchus, as conventional practice in our bronchoscopy suite. Macroscopically, biopsy specimens were described as small, moderate, or large if the tissue was smaller than the cup of the forceps, filled the cup, or was larger than the forceps cup, respectively. At least four moderate- or large-sized EBB samples were obtained. Additional procedures, including EBUS-TBNA and TBLB, were performed based on the operator's decision using standard techniques described previously (12-17). We observed subjects for at least four hours after the procedure. In cases where TBLB was additionally performed, post-procedure chest radiography was performed to exclude pneumothorax. Subjects were instructed to report back to the hospital if they developed symptoms such as breathlessness, chest pain, hemoptysis, or any other significant symptom.

Specimen preparation

Biopsy specimens were placed in 10% formalin solution and sent for histopathological examination and Ziehl-Neelsen stain. Lymph node aspirates and lung biopsy samples were processed appropriately (7, 17).

Diagnosis of sarcoidosis

We diagnosed sarcoidosis on consistent clinical and radiological findings, and the presence of non-necrotizing granulomas in any of the tissue samples, once other causes of granulomatous inflammation were excluded. In the absence of documented granulomatous inflammation, sarcoidosis was diagnosed if the clinical and radiologic manifestations were consistent with sarcoidosis and the subject improved in the next six months without any intervention or with glucocorticoid treatment (18, 19).

Outcomes

The primary outcome was the diagnostic yield of EBB, defined as the presence of granulomatous inflammation in the biopsied bronchial mucosa in subjects diagnosed finally as having sarcoidosis. The secondary outcomes were (a) procedure-related complications; and (b) procedure time (from the time the bronchoscope was inserted into the trachea until the last EBB was performed). Procedural complications were recorded as bleeding, hypoxemia, and others. Bleeding was classified as no bleeding if there were only blood traces with spontaneous cessation of bleeding; mild bleeding if repeated suction was required; moderate bleeding if the bronchoscope needed to be wedged into the bleeding segment for tamponade, or if intrabronchial adrenaline or cold saline was required for hemostasis; and severe bleeding if a bronchial blocker or fibrin was required for hemostasis. The complication was also considered severe if the subject required fluid resuscitation, blood transfusion, intensive care unit admission, mechanical ventilation, or resulted in death (6).

Sample size calculation

Assuming an effect size of 0.3, we estimated that 134 subjects would be required for a power of 80% and an alpha error of 5%. We chose a sample size of 150 subjects to compensate for attrition.

Statistical analysis

We performed statistical analysis using Statistical Package for Social Sciences version 23.0 (SPSS Inc., Chicago, IL, USA). Summary statistics, including mean (standard deviation [SD]), median (interquartile range [IQR]), and number (percentage), were used to express descriptive data. We analyzed differences between continuous variables using the Mann-Whitney U or the student's t-test (normally distributed). The chi-square or Fisher's exact test was used to analyze the difference between categorical variables. A p-value <0.05 was considered statistically significant.

Results

We screened 171 subjects (Figure 1) and included 150 (mean age, 43.1 years; 53.3% men). Thoracic lymph node enlargement on the chest CT without parenchymal involvement was seen in 68/150 (45.3%) of subjects, while 56/150 (37.3%) had both the abnormalities (Table 1). Seventy-five subjects each underwent EBB under real-time visualization with NBI plus WLB (intervention group) or WLB alone (control group). There was no difference in the number and size of the biopsy samples obtained in the two groups. Sarcoidosis was diagnosed

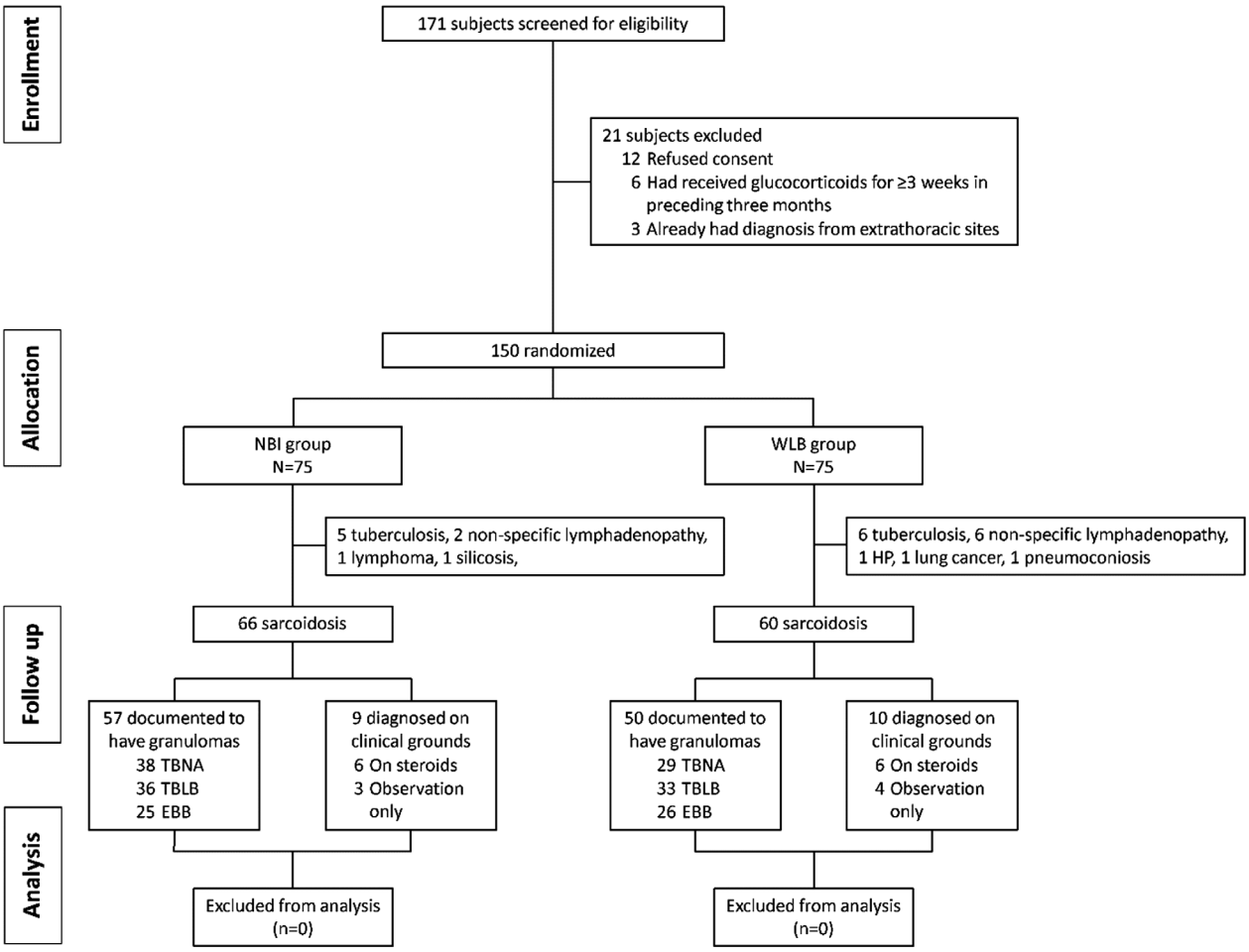

Figure 1. Study participant flow. *Abbreviations:* EBB-endobronchial biopsy, NBI-narrow band imaging, TBLB-transbronchial lung biopsy, TBNA-transbronchial needle aspiration, WLB-white light bronchoscopy.

in 126/150 subjects (66 and 60 in the NBI plus WLB and WLB groups, respectively). Eleven subjects were diagnosed with tuberculosis, 8 had nonspecific lymph node enlargement, and 5 had other diagnoses. Of the 126 subjects with sarcoidosis, granulomas were demonstrated by EBB in 51 (40.5%). There was no difference (p=0.53) in the diagnostic yield of EBB between the NBI plus WLB (25/66, 37.9%) and the WLB (26/60, 43.3%) groups (Table 2). The diagnostic yield was the highest in those with CT stage IV (8/12, 66.7%) and stage III (6/11, 54.5%) disease, while subjects with stage I (16/55, 29.1%) and II (21/48, 43.8%) disease had lower yields (p=0.06). Of the 126 subjects finally diagnosed to have sarcoidosis, TBLB and EBUS-TBNA were additionally performed in 115 (91.3%) and 98 (77.8%) subjects, respectively. In subjects who underwent TBLB and EBUS-TBNA, granulomatous inflammation was seen in 69/115 (60%) and 68/98 (69.4%) subjects, respectively. Nodules were seen in 32/126 (25.4%) subjects using WLB (combined data of both groups). In the presence of nodules, the granuloma yield of EBB was 71.9% (23/32 subjects). If nodules were not seen, 28/94 (29.8%) subjects had granulomas on EBB histology. In the NBI plus WLB group, while examining under WLB, 14/66 (21.2%) subjects had airway nodules; 9/14 (64.3%) subjects had granulomas on EBB. With the NBI mode, in 11 of these 14 (78.6%) cases, nodule visualization was distinctly enhanced due to better contrast. Also, airway nodules could be identified in five additional cases. Thus, 19/66 (28.8%) subjects had airway nodules on NBI visualization,

Table 1. Baseline characteristics of the study population

	WLB (n=75)	NBI (n=75)	Total (n=150)	P value
Age in years, mean (SD)	44.8 ± 11.7	41.4 ± 10.5	43.1 ± 11.2	0.06
Male sex	36 (48.0)	44 (58.7)	80 (53.3)	0.19
Smoker	3 (4.0)	7 (9.3)	10 (6.7)	0.19
Comorbidities				
Diabetes Mellitus	3 (4.0)	4 (5.3)	7 (4.7)	1.00
Hypertension	7 (9.3)	2 (2.7)	9 (6.0)	0.17
Coronary Artery Disease	1 (1.3)	0 (0)	1 (0.7)	1.00
Chronic Kidney Disease	0 (0)	2 (2.7)	2 (1.3)	0.50
Hypothyroidism	5 (6.7)	3 (4.0)	8 (5.3)	0.72
Findings on chest CT				
Thoracic LNE only	34 (45.3)	34 (45.3)	68 (45.3)	0.70
Thoracic LNE and lung abnormalities	30 (40.0)	26 (34.7)	56 (37.3)	
Lung abnormalities only	6 (8.0)	6 (8.0)	12 (8.0)	
Fibrotic lung abnormalities	5 (6.7)	9 (12.0)	14 (9.3)	
Number of EBB attempts	5 (5-7)	5 (4-6)	5 (4-6)	0.37
Number of EBB specimens	5 (4-5)	4 (4-5)	5 (4-5)	0.33
EBB size				
Small	1 (0-2)	0 (0-2)	0.5 (0-2)	0.57
Moderate-large	4 (4-4)	4 (4-4)	4 (4-4)	0.61
Final diagnosis				
Sarcoidosis	60 (80.0)	66 (88.0)	126 (84.0)	0.46
TB	6 (8.0)	5 (6.7)	11 (7.3)	
Nonspecific LNE	6 (8.0)	2 (2.7)	8 (5.3)	
Others*	3 (4.0)	2 (2.7)	5 (3.3)	

Abbreviations: CT-computed tomography, EBB-endobronchial biopsy, IQR-interquartile range, LNE-lymph node enlargement, NBI-narrow band imaging, SD-standard deviation, WLB-white light bronchoscopy. All the values are represented as number (percentage), mean ± standard deviation, or median (interquartile range). *Other diagnoses included hypersensitivity pneumonitis, lung cancer, lymphoma, pneumoconiosis, and silicosis.

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

	WLB (n=60)	NBI (n=66)	Total (n=126)	P value
Primary outcome				
Diagnostic yield of EBB	26 (43.3)	25 (37.9)	51 (40.5)	0.53
Secondary outcomes				
Procedure duration, minutes	5.7 ± 1.7	6.3 ± 2.2	6.0 ± 1.9	0.06
Complications				
Bleeding	0	1 (1.5)	1 (0.8)	0.34
Hypoxemia	2 (3.3)	2 (3.0)	4 (3.2)	0.92
Pneumothorax	0	2 (3.0)	2 (1.6)	0.17

All the values are represented as number (percentage). EBB-endobronchial biopsy

12 (63.2%) of whom showed granulomas on EBB. Of these 19 subjects, 13 had hypovascular nodules, five had normovascular nodules, and one had hypervascular nodules. Thirteen (27.7%) of 47 subjects without nodules on NBI had granulomas on EBB histology. There was no difference (p=0.06) in the duration of the EBB procedure between the two groups (Table 2). There was also no difference in the incidence of procedure-related complications between the study groups. Moderate bleeding occurred in one subject in the NBI plus WLB and none in the WLB group (p=0.34). Hypoxemia occurred in two subjects in each group. Two subjects, both in the NBI plus WLB group, had pneumothorax attributable to TBLB. The median doses of midazolam (2 mg in either group, p=0.29) and fentanyl (50 μg in either group, p=0.64) used for sedation were similar in the study groups.

Discussion

We found that EBB using a combination of NBI and WLB did not result in a higher yield than EBB performed using WLB alone. In subjects with airway nodules on WLB, NBI highlighted them better in 79% of cases. NBI also helped identify nodules in five additional cases where WLB failed to reveal them. The NBI technique works by accentuating the contrast of the mucosal and submucosal blood vessels using two narrow bands of light with wavelengths of 390-445 nm and 530-550 nm (20). Its major use in bronchoscopy is to identify areas of bronchial mucosal dysplasia and carcinoma in situ (8, 21). Few reports of NBI use exist in sarcoidosis (22-24). An observational study recently suggested that NBI helps visualize airway mucosal nodules with better contrast in sarcoidosis and might reveal abnormalities not identified by WLB (9). It was hypothesized that NBI might identify areas appropriate for performing EBB with greater odds of finding granulomas. We planned the current randomized trial to test this hypothesis. We did not find a superiority of the NBI plus WLB mode over the conventionally used WLB in the yield of granulomas from mucosal biopsy. We propose a few reasons to explain these findings. One, airway mucosal involvement is mostly diffuse in sarcoidosis (25, 26). It is thus mostly recognized under white light itself. Although NBI improves contrast and visualizes nodules better, it does not significantly increase the identification of 'true' additional nodules that are not seen with WLB. Sometimes, certain focal mucosal irregularities do give an impression of nodules in the NBI mode, but their significance is unclear. Second, when EBB is performed under real-time NBI visualization, even minor bleeding degrades the vision significantly and makes the procedure difficult, thus potentially affecting the yield. Thirdly, EBB can reveal granulomas in about 30% of the patients with microscopic involvement even in the absence of visible mucosal abnormalities (26, 27). Thus, theoretically, a bronchoscopic mode with an enhanced visual resolution could improve endoscopic detection of mucosal nodularity due to granulomatous inflammation. However, NBI only highlights the vasculature of the airway mucosa without increasing the resolution. Due to differential visualization of the vasculature, NBI only improves contrast to make the already visible nodules have better delineation from the background. Clearly, one cannot avoid bronchial mucosal biopsy even if the mucosa appears normal on WLB as well as NBI, as it can still yield granulomas. Interestingly, subjects with stage III and IV disease had numerically higher diagnostic yields on bronchial mucosal biopsy than those with stage I or II disease. This might be a chance finding due to the smaller number of subjects with stage III or IV disease. Alternatively, it is possible that the bronchial mucosa gets more frequently involved with higher radiologic stages of disease. What are the clinical implications of this study? Although NBI looked promising in a recent exploratory study, the current study excludes a significant benefit of NBI technology in improving yields of airway mucosal biopsy in sarcoidosis (9). Given the potential additional cost of acquiring this mode, it cannot be recommended routinely for this purpose. Also, performing EBB under direct NBI guidance might worsen the bronchoscopic image in the presence of minimal blood and should not be routinely used, especially if there is bleeding after the first attempt at biopsy. However, as NBI offers better contrast to the nodules in several cases, it might be used to better visualize the involved mucosa before attempting a biopsy. We suggest that NBI be used in bronchoscopy suites where it is already available and does not inflate the procedure cost. Besides, tools for better visualization of the bronchial mucosa, cryobiopsy has recently been proven to be useful for improving diagnostic yield in sarcoidosis. In a study, EBUS-transbronchial mediastinal node cryobiopsy was found to have a diagnostic yield of 92.8% compared to 78.5 %

with EBUS-TBNA (28). Another study found that the histological diagnosis of sarcoidosis was made significantly more often by transbronchial lung cryobiopsy than by TBLB with forceps (29). Our study has a few limitations. It was a single-center study at a tertiary teaching hospital with a small sample size. Several operators (consultants and fellows) performed the procedure. The same design can also be viewed as a strength, as it makes the study pragmatic and comparable to the real world. In conclusion, performing EBB under NBI guidance did not increase the yield of granulomas acquired from airway mucosa in sarcoidosis patients. A multicenter study in the future could help confirm these findings.

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