

ORIGINAL RESEARCH

BRONCHOSCOPIC INTERVENTION AND MOLECULAR DIAGNOSTICS: SYNERGISTIC TOOLS IN A PULMONOLOGIST'S ARMAMENTARIUM AGAINST TUBERCULOSIS

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ABSTRACT

Background: Mycobacterium tuberculosis complex is the causative organism of tuberculosis, it is a major health problem throughout the world. In developing countries like India, almost 25% of adult deaths which are avoidable are caused by it.

Around 22-61% of Cases have smear negative but culture positive state where clinical profile and radiological lesions suggest diagnosis of pulmonary tuberculosis, then initiation of anti-tubercular drugs is not advisable without meticulous search for tubercular bacilli.

Gold standard for diagnosis of tuberculosis is culture of sputum, but it takes long time(45 days) to perform.

Aim: Evaluation of bronchoalveolar lavage fluid in clinically and radiologically suspected cases of sputum smear negative pulmonary tuberculosis.

Methodology: In our observational, cross sectional study done in the Department of Respiratory Medicine, NIMS involving all the patients attending indoor and outdoor services in one year period from January 2019 to June 2020, we tried to access the diagnostic yield of bronchoalveolar lavage fluid in clinically and radiologically suspected cases of sputum smear negative pulmonary tuberculosis. Then the Broncholaveolar Lavage (BAL) fluid specimen was sent for smear for AFB, CBNAAT and BACTEC culture for Mycobacterium tuberculosis.

Result: In this study, pulmonary infiltrate (54.2 %) was most common radiological finding in their chest x-ray, followed by cavity (31.2%). 17 patients had nodular shadow (8.9%) and only 11 patients had miliary pattern (5.7%). Out of 190 cases, 156 patients had unilateral

involvement of lung (82.2%) and only 34 cases had bilateral involvement (17.8%). Most of the patients had right upper zone (58.4%) involvement followed by left upper zone (12.2%) with involvement of lower lung field in only 4.2%.

Conclusion: To conclude bronchoalveolar lavage obtained by fiber optic bronchoscopy is a relatively safe and useful procedure for diagnosis of suspected pulmonary tuberculosis cases when smears of these patients does not reveal mycobacterium tuberculosis.

Key Words: Mycobacterium Tuberculosis, Bronchoalveolar lavage, fiberoptic bronchoscopy

INTRODUCTION

Tuberculosis is caused by the Mycobacterium tuberculosis Complex, this complex includes *M. tuberculosis*, *M. microti*, *M. africanum*, *M. bovis* and *M. canetti*.¹ In most of the cases tuberculosis is caused by *Mycobacterium tuberculosis*. The route of transmission of infection is mainly respiratory and is through inhalation of droplet nuclei.² Therefore, primary site of infection is lung and is also the most commonly involved organ.

In India, burden of this disease is heightened by the fact that more than 40% of population is infected with TB bacilli. Severity can be judged by the fact that approximately 18 lakh people develop Tb and nearly 4 lakh die from it every year. Both incidence and mortality of tuberculosis is highest among the adults aged 15 to 60 years.³ Data revealed that in 2006, treatment was given to 1.4 million cases of tuberculosis and among these about 28.7% people were categorized as new sputum smear negative tuberculosis cases.⁴

TRC estimated that around 3.8 million (95% C.I: 2.8-4.7) bacillary pulmonary tuberculosis cases and 12.9 million (95% C.I: 9.7-16.0) smear as well as culture negative cases in whom chest X-ray were found abnormal. The “chest x-ray abnormal” include patients who have negative sputum by smear as well as culture, but whose chest x-ray was read by two independent readers as possible or probable tuberculosis.⁵

In India's Revised National Tuberculosis Control Program (RNTCP)^{6,7} the main methods to diagnose pulmonary tuberculosis are chest x-ray, sputum smear microscopy and culture of *Mycobacterium tuberculosis* bacilli. Among these, sputum microscopy is the primary method to diagnose tuberculosis, as it is less expensive, more specific as it has less inter-reader variability than chest x-ray. Also, sputum microscopy can be used for monitoring and defining cure. It is feasible at peripheral health institutions; at the same time it correlates with infectivity in undiagnosed pulmonary tuberculosis cases.

Most of the centers show only 16-50% of sputum smear positivity of tuberculosis and in a larger proportion of cases even though clinical and radiological picture are highly suggestive of tuberculosis, the sputum smear stays negative.⁸ In 22% to 61% of cases where clinical profile and radiological lesion being consistent with diagnosis of pulmonary tuberculosis, sputum smear negative but culture positive state has been observed.⁹

Though culture of sputum for mycobacterium tuberculosis is gold standard for diagnosis of tuberculosis but it takes long time (45 days) to perform and no other proper serological test is available in market to compensate this thus a valuable time is lost. In these sputum smear

negative cases fiberoptic bronchoscopy has been tried for rapid diagnosis. Fiberoptic bronchoscopy guided lavage is less expensive, better tolerated, and less invasive and its uses have been well studied.¹⁰ In our study, we evaluated the yield of bronchoalveolar lavage fluid in clinically and radiologically suspected cases of sputum smear negative pulmonary tuberculosis.

MATERIAL AND METHOD

This study was conducted at the Department of Respiratory Medicine, National Institute of Medical Sciences (NIMS), Jaipur, Rajasthan, India with the aim to assess the role of fibreoptic bronchoscopy in the diagnosis of sputum smear negative pulmonary tuberculosis cases. The main objectives of the study were to evaluate the diagnostic yield of bronchoalveolar lavage (BAL) fluid for AFB smear, Cartridge Based Nucleic Acid Amplification Test (CBNAAT) (**Cepheid Systems, USA**) and BACTEC Culture (**Becton Dickinson and Company, USA**) in the diagnosis of tuberculosis in such cases.

All indoor and outdoor patients of any gender, age fifteen years or above, with history and clinic-radiological features highly suggestive of pulmonary tuberculosis but sputum smear for Acid Fast Bacilli (AFB) done two times in number was negative by Ziehl – Neelsen staining method under RNTCP, were included. Patients with Sputum smear for AFB positive, severe dyspnea, diagnosed extra pulmonary tuberculosis, unstable cardiovascular status (Arrhythmia and angina), uncooperative, immunocompromised patients, and those with bleeding disorders and coagulopathies were included. Study period was one & a half year (January 2019-June 2020).

Purposive sampling was done for this cross sectional, observational study. All consenting patients were clinically evaluated and their radiological investigations (suggestive of TB) and sputum smear negative reports were checked. Patients with features of presumptive diagnosis of pulmonary tuberculosis were then prepared for Flexible Fiber-optic Bronchoscopy under local anesthesia (Lignocaine).

Flexible fiber-optic bronchoscopy was carried out after informed written consent through trans-nasal route

in supine position with continuous monitoring of blood pressure, ECG and pulse oximetry. During the procedure adequate local anaesthesia is obtained with lignocaine.

After viewing the bronchial tree, tip of the bronchoscope was wedged into a segmental or subsegmental bronchus thought to subtend the area of interest. Approx 60 ml isotonic saline (given as two ~30 ml aliquots) was injected down the internal channel of the bronchoscope and immediately retrieved about 15 ml of fluid into the suction trap with low pressure suction (bronchoalveolar lavage fluid). The procedure causes minimal cough while the patients were observed for hemoptysis, fever, cardiac arrhythmia for next 24 hours. Then the Broncholaveolar Lavage (BAL) fluid specimen was sent for smear for AFB, CBNAAT and BACTEC culture for Mycobacterium tuberculosis.

RESULTS

A total of 190 patients were studied who fulfilled the inclusion criteria were enrolled in this study from January 2019 to June 2020. All patients tolerated the procedure well. Apart from sinus tachycardia, none of the patients had any procedural or post-procedural complications.

Table 1: Distribution of the population according to various study parameters

S.No.	PARAMETER		Number of Patients (n=190)	PERCENTAGE
1.	Gender	Male	142	74.7%
		Female	48	25.3%
2.	Age in years	0-10	0	0%
		11-20	10	5.3%
		21-30	58	30.5%
		31-40	40	21.0%
		41-50	32	16.8%
		51-60	23	12.1%
		>61	27	14.3%
3.	Area	Rural	152	80%
		Urban	38	20.0%
4.	Symptoms	Cough/expectoration	168	88 %
		Fever	163	85.7 %
		Hemoptysis	73	38.5 %
		Chest pain	33	17.2 %
		Shortness of breath	23	12.1 %
		Heaviness of chest	6	3.1 %

In this study, out of 190 patients, 142 were male (74.7%) and 48 were females (25.3%). Male: female ratio was 3:1. 101 (53.2%) patients were of age group 21-40 years and only 27 (14.2%) patients were >60 years. 152 were from rural area (80%) and 38 were from urban area (20.0%). Cough was the most common symptom (88.0%) followed by fever (85.7%). Hemoptysis (38.5%) and chest pain (17.2%) were the next common symptoms. Heaviness of chest (3.0%) was the least common symptom.

Table 2: Distribution of patients as per chest radiological findings in the study.

S.No.	Radiological Finding		Frequency (n=190)	Percentage
1.	Radiological pattern	Pulmonary infiltrate	103	54.2%
		Cavity	59	31.2%
		Nodular shadow	17	8.9 %
		Miliary pattern	11	5.7%
2.	Site of involvement	Unilateral	156	82.2%
		Bilateral	34	17.8%
3.	Extent of involvement in chest X-ray	Right upper zone	111	58.4 %
		Left upper zone	23	12.2%
		Right mid zone	17	8.9%
		Left mid zone	3	1.6%
		Lower lung field	8	4.2%
		Diffuse parenchymal involvement	28	14.7%

In our study, pulmonary infiltrate (54.2 %) was most common radiological finding in their chest x-ray, followed by cavity (31.2%). 17 patients had nodular shadow (8.9%) and only 11 patients had miliary pattern (5.7%). Out of 190 cases, 156 patients had unilateral involvement of lung (82.2%) and only 34 cases had bilateral involvement (17.8%). Most of the patients had right upper zone (58.4%) involvement followed by left upper zone (12.2%) with involvement of lower lung field in only 4.2%.

Table 3: BAL fluid for AFB smear and BACTEC culture positivity in the study group (n=190)

BAL FLUID	NUMBER OF POSITIVE CASES	PERCENTAGE
AFB smear	33 (33/190)	17.3%
BACTEC culture	49 (49/190)	25.7%

In our study, out of 190 cases, after analysis of the reports of BAL fluid, it was found that AFB was positive in 33 cases (17.3%) and BACTEC culture was positive in 49 cases (25.7%).

Table 4:- CBNAAT data in study population

	CBNAAT			
	Mycobacterium TB		Rifampicin Resistance	
	Detected	Not detected	Detected	Not detected
Male (n-142)	66	76	10	132
Female (n- 48)	10	38	1	47

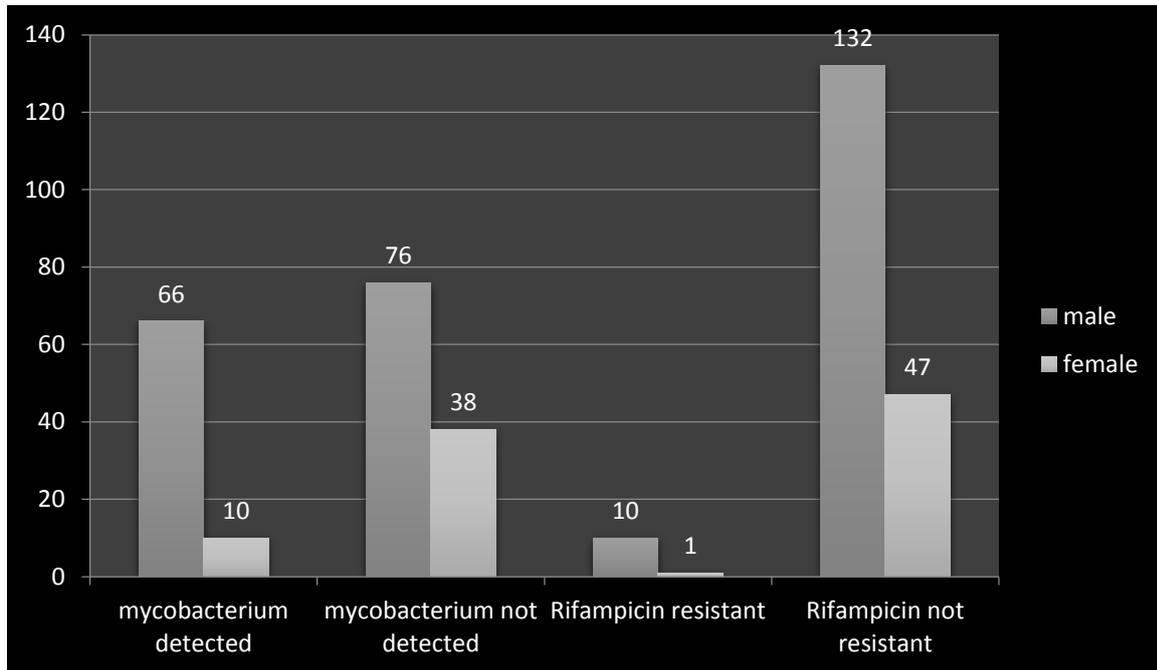


Figure 1: - CBNAAT data

In our study mycobacterium TB was detected in 66 males (34.7%) and 10 females (5.2%) while rifampicin was resistant in 10 males (5.2%) and 1 female (0.52%) out of 190 cases. (Table 4 & Figure 1).

Discussion

In our study, male patients outnumbered female patients. All patients with age from 15-70 years were included in this study with 142 males and 48 females. No definitive data regarding gender involvement is available till date but a study done in Brazil and majority of authors showed greater incidence of sputum positive pulmonary tuberculosis in males only.^{11,12} So, our study showed sputum smear negative cases shows similar result of gender involvement in sputum smear positive cases.

Tuberculosis is common among elderly in developed countries, but in developing countries it involves younger population. In recent time, trend towards increasing age being significant when compared to 20 years ago.¹³ In a Scotland study, in 1993, 64% of patients of tuberculosis were of age over 55 years, as compared to Asian patients where 85% were under 55 years.¹⁴ A study done in Pakistan, involving 5023 Pulmonary Tuberculosis cases, showed TB mainly affects people between 15 to 59 years of age, accounting 75% of the cases.¹⁵ In our study least age involved was of 15 years with highest being 70 years.

This study showed higher prevalence in the rural population (80%) then in urban population (20.0%). This data is similar with the findings of National Family Health Survey (NFHS-3) which showed higher prevalence in rural area (469 vs. 307 per 100000 population).¹⁶ A study did by Raina et al¹⁷ showed poverty, illiteracy etc to be a major factor for developing

tuberculosis in rural population. In rural population overcrowding also has a contributory role.

Individuals with pulmonary tuberculosis who come to hospitals to seek treatment presents with symptoms like cough in 70-90%, fever 15-52%, weight loss in 43-75%, hemoptysis among 21-29% and fatigue and malaise in 58%.^{18,19,20,21,22} In our study cough (88%) followed by fever (85.7%) was the most common symptom. Other studies done showed fever is the most common symptom. Fever in patients with tuberculosis varies from 37 to 80% as shown in different studies.^{23,24} In one study, it showed 21% of patients had no fever in the entire hospitalization period for tuberculosis⁴⁶. In other studies it showed cough is the most frequent symptom.^{25,26}

In this study we found pulmonary lesions in all of the cases. Among these, pulmonary infiltrates were most common finding. Even though in our study pulmonary infiltrate were present in 54.2 % of cases but when cavity lesions gets combined by pulmonary infiltrate lesions , it accounts for 85.4% cases. In a study done by Aktogu et al²² also showed pulmonary infiltrate as most common finding (in 99.0% of total cases). In chest x-ray when cavities are present, it is considered as an important radiological evidence to suspect tuberculosis in adults.²⁷ In literature , frequency of appearance of cavity in chest varies from 40-80%^{22,28,29}. In our study , cavity lesion was present in 31.2% of cases. A study done by Nyman et al³⁰ showed cavities in 13.9% of their 215 cases.

In our study, miliary pattern was present in 5.7% of the total cases. Miliary form may present in post primary cases also in 7% of cases^{22,31,32}. The nodule form is found in least number of cases of tuberculosis in adults, it may calcify in time. In study done by Nyman et al³⁰ showed 7% of 214 cases. In other study done by Khan et al³¹ showed nodular lesions in 9% of 88 cases of pulmonary tuberculosis. In our study, we did not found any lymphadenopathy in the chest x-ray of any case. In studies done in 204 and 500 cases , the site of cavity lesion were found to involve posterior and or apical segments of upper lobe in 83%-85% cases and superior segment of lower lobe was involved in 11%-14% cases^{33,34}. In majority of cases , parenchymal involvement was present^{35,36}. In our study, right upper zone was involved in 58.4% cases. Diffuse parenchymal involvement was seen in 14.7% cases and lower lung field was involved in only 4.2% of cases.

Therefore these patients who have clinical presentation and radiological findings of pulmonary tuberculosis but are AFB sputum negative are a real challenge to the physician ,as to whether to start anti-tubercular drugs or not to patient. If not treated properly, 75% of these patients develop active tuberculosis in next 5 years or so.³⁷ In countries where prevalence of tuberculosis is high, like India, patients who have pulmonary lesions suggestive of tuberculosis but are AFB sputum negative should be treated with anti-tubercular drugs. This can be helpful in most of the cases as it avoids invasive diagnostic procedure in future. But this approach can lead to poor outcome if started in non-tuberculosis patients like in bronchogenic carcinoma.

Bronchoscopy and other procedure like bronchoalveolar lavage, bronchial brushing, bronchial aspirate, transbronchial biopsy and post bronchoscopy sputum examination can be used as an alternative to reach diagnosis. Bronchoalveolar lavage method is considered as the best specimen for diagnosis of pulmonary tuberculosis³⁸. In a study done by Caminero et al³⁹ showed that BAL should be done as a routine procedure in patients who have no

expectoration and are sputum negative smear as it is simple, safe. The diagnostic yield of overall bronchoscopic procedure in this study for sputum negative pulmonary tuberculosis was 25.7% (49/190) and AFB positivity in BAL fluid was 17.3 % (33/190). Although BAL gave a diagnostic yield of about 25.7% but its role in early diagnosis is very limited because smears for acid fast bacilli were positive in 17.3% cases only.

A study done by Charoenratanakul et al⁴⁰ showed diagnostic yield of positive BAL smear and mycobacterium culture in 7.5% (3/40) and 15% (6/40) respectively in sputum negative patients. This result is similar to our study. In another study done by Vijayan et al⁴¹ showed that pre bronchoscopy sputum culture was positive in 33/71 cases (46.5%) , while BAL fluid culture was positive in 24/71 cases (34%) only. Only three patients showed positive BAL smears and in these patients sputum and BAL culture also came positive. Study done by Kennedy et al⁴² also showed similar result. He also showed that in only 38% cases , it is possible to confirm sputum negative pulmonary tuberculosis by all other bronchoscopic procedures.

A study done by Panda et al⁴³ on 100 cases who were sputum smear negative pulmonary tuberculosis reported that bronchoalveolar lavage fluid when examined for AFB by smear and culture test showed 12 and 19 cases respectively including 2 by smear and 9 by culture alone. Baughman et al⁴⁴ did a retrospective study of 50 patients and showed sensitivity of bronchial fluid smear and culture positivity as 68% and 92% respectively. Another study done by Chan et al⁴⁵ showed Bal smear and culture positivity in 14% (4/28) and 50% (14/28) cases respectively.

A Study done by Purohit et al⁴⁶ in which he did fiber optic bronchoscopy in 50 patients , and sent bronchial fluid for AFB smear and culture where AFB smear came positive in 12% of cases and culture came positive in 35% of patients. A study of Mohan et al⁴⁷ done on 50 cases who were HIV negative, showed that 22 out of 50 cases showed positivity in BAL fluid when done by SSN-PTB thus showed that bacteriological diagnosis can be confirmed by SSN-PTB.

Sarkar et al⁴⁸ did fiber optic bronchoscopy in 30 cases who were suspected of tuberculosis on the basis of clinical and radiological findings. All of them were sputum smear negative or were producing no sputum. This study showed that immediate diagnosis can be made in 22/30 (73%) cases and definitive diagnosis in 26/30 (87%) cases. Kulpati and Hira⁸ found in their study that fiber optic bronchoscopy is useful in making diagnosis in 25/33 patients, but who are sputum smear negative on three occasions. A prospective study of 30 patients done by Kamal et al¹¹⁵ showed that BAL fluid was positive in 9 cases for Z-N stain and BAL culture for AFB on Lowenstein- Jensen medium was positive in 18 cases .

According to RNTCP guidelines CBNAAT used for the detection of drug resistance in those patients who are at risk. In a study done by Bavesh et al⁴⁹ mycobacterium was detected in 42.22% and rifampicin resistance was found in 15.75% of cases which is quite similar to our study where mycobacterium tuberculosis was detected in 40% of cases and rifampicin resistance was detected in 5.78%. Sputum smear negative pulmonary tuberculosis is a paucibacillary condition, and the use of saline dilutes the epithelial lining of fluid which may cause low yield from BAL specimens. Another reason for low yield might be the use of local anesthetic which is used during the procedure.

There is a limitation in this study as we have not done pre and post bronchoscopy sputum culture and transbronchial biopsy. If these were done then they could have augmented the diagnostic yield of bronchoscopy in this study.

Tachycardia was the most common complication encountered during and after the procedure. Thus, fiber optic bronchoscopy and BAL fluid analysis are safe, invasive procedure for sputum smear negative pulmonary tuberculosis. To avoid cross contamination and infections, all the guidelines laid by American college of Chest physician and American Association of Bronchology were strictly followed.⁵⁰

CONCLUSION

It can be safely concluded from our study that Bronchoalveolar lavage (BAL) obtained by fiber optic bronchoscopy is a relatively safe and useful procedure for diagnosis of suspected pulmonary tuberculosis cases when smears of these patients does not reveal mycobacterium tuberculosis. To enhance yield of bronchoalveolar lavage, it should be combined with transbronchial lung biopsy and post bronchoscopy sputum sample should be sent for culture of mycobacterium tuberculosis.

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