Original Article

Diagnosis and treatment of pulmonary tuberculosis in one day: Way forward for END TB Strategy 2015

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Abstract

Background: According to Revised National Tuberculosis Control Program (RNTCP), diagnosis of pulmonary tuberculosis (TB) in India requires examination of two sputum samples collected over 2 days, that is, "spot" and next day "morning" samples. **Objective:** To assess the feasibility of diagnosing pulmonary TB by examining two spot sputum samples in 1 day and to compare this approach with the current RNTCP protocol. **Materials and Method:** A total of 375 subjects having cough >2 weeks were enrolled into the study. Three sputum samples were collected from each of the study participant; first spot (S1), second extra-spot (S2) sample 1 h after collection of the first sample, and third morning (M) sample collected next day morning. These specimens were subjected to standard sputum smear microscopy for acid-fast bacilli as per RNTCP guidelines. For 1-day protocol, results of "S1 and S2" samples and for 2-day protocol results of "S1 and M" samples were considered. **Results:** The number of sputum-positive pulmonary TB cases diagnosed with standard 2-day protocol was 119, whereas the experimental 1-day protocol diagnosed 120 cases ($P = 0.7$). Comparing with standard 2-day protocol, this new 1-day protocol had sensitivity 98.32%, specificity 100%, positive predictive value 100%, and negative predictive value 99.17%. **Conclusion:** Single-day method can be adopted as the standard diagnostic approach for pulmonary TB after large-scale multicenter randomized controlled trials.

Keywords: Acid-fast bacillus, *Mycobacterium tuberculosis*, pulmonary tuberculosis, sputum microscopy, Ziehl–Neelsen stain

Introduction

Diagnosis of pulmonary tuberculosis (TB) in low-income, high-burden countries often relies on direct sputum smear microscopy for acid-fast bacillus (AFB). Since the policy change in Revised National Tuberculosis Control Program (RNTCP) in April 2009, diagnosis of pulmonary TB in India requires smear microscopy examination of two sputum samples: one spot and another morning sample, switching from earlier three sputum sample collection over 2 days.[1] From TB program point of view, this approach saves time and cost while providing similar diagnostic efficacy.[2-5] However, the patients still have to come to health center on 2 consecutive days; the time and economic savings for the patient appears negligible.[6] World Health Organization (WHO) in its policy statement of May 2011 has advocated for implementation of single-day approach for diagnosis of pulmonary TB in countries which have successfully implemented the two sputum specimens' case finding strategy, especially in settings where patients are likely to default from diagnostic process.[7] This study was conducted with an objective to assess the feasibility of diagnosing pulmonary TB by examining two spot sputum samples in 1 day and to compare this approach with the current RNTCP protocol.

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Table 1: Comparison of diagnostic efficacy of 1-day vs 2-day protocol

Protocol	Subjects (*N'*)	Smear-negative	Smear-positive (*n*)	Total smear positives in study (*N*)	% of cases diagnosed (*n*/*N*)
2-Day protocol (D2)	357	238	119	123	96.75
1-Day protocol (D1)	375	255	120		97.56

N': total number of subjects in the protocol; n: number of smear-positive pulmonary tuberculosis cases diagnosed by the protocol; *N*: total number of smear-positive pulmonary tuberculosis cases in the study

Table 2: Comparison of 1-day vs 2-day protocol

Protocol	Positive	Negative	*P*
2-Day protocol (D2)	119	4	0.7
1-Day protocol (D1)	120	3	

Materials and Methods

This study was conducted in the Department of Pulmonary Medicine, SCB Medical College, between September 2010 and August 2012. It was a cross-sectional study. Patients attending the outpatient department with cough for more than 2 weeks were recruited into the study. The study participants included referred patients from different primary health centers and patients coming directly to this hospital. Accordingly, the duration of cough varied from minimum requisite for this study 2 weeks to maximum 40 weeks. They were informed about the nature of the study in their own language and a verbal consent was taken. Those who had previously taken antitubercular therapy for more than 1 month and those who did not give consent were excluded from the study. A detailed clinical history was taken followed by thorough clinical examination for each study participant. Routine blood investigations and chest X-rays were done to study the clinical–radiological–microbiological associations. Subsequently, they were asked to collect and submit three sputum samples: first a spot sample (S1), second an extra-spot sample (S2) collected 1 h after the first sample, and the third sample (M) collected on the next day early morning. To ensure optimum sample quality, the method of sputum collection was demonstrated to the study participants by a trained personnel with the aid of visual display board and written instructions whenever necessary. Spot samples were collected under the direct supervision of the laboratory technicians. When the patients coughed up only saliva or did not produce at least 2 ml of sputum, they were encouraged to give another better specimen. The smear preparation, Ziehl–Neelsen (ZN) staining, and microscopy were done according to RNTCP guidelines, but in a blinded manner by the RNTCP-trained technician. The three sputum samples collected from each study participant were given a random code. The microscopy technician and the researchers were unaware which sample belonged to which subject. Any one sample positive for AFB was considered as a case of pulmonary TB. The performance of 1-day protocol was assessed by the results of spot (S1) and extra-spot (S2) samples and the 2-day protocol was assessed with the results of spot (S1) and morning (M) samples. Data were entered and analyzed in Epi Info version 2007. Categorical variables were expressed regarding numbers and proportions. Chi-square test was used for showing an association. $P < 0.05$ was considered significant.

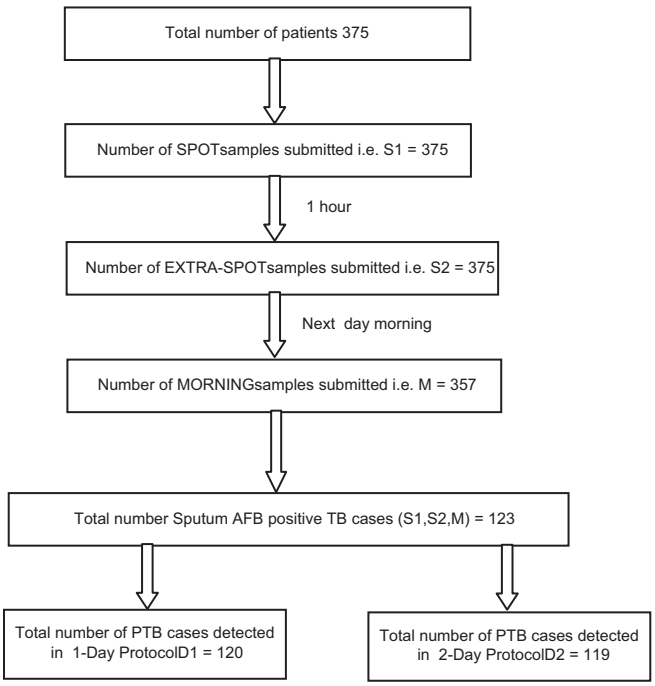

Figure 1: Patients flowchart

Results

The total number of study participants was 375. The majority (74.7%) were males (M: F = 2.95:1). The maximum number of patients (40.6%) belonged to the age group 21–40 years. About 60.8% of the subjects belonged to below poverty line category. The total number of spot and extra-spot samples collected was 375 each. In all, 18 of these 375 patients defaulted in submission of next day morning samples, that is, the total number of morning sputum samples collected was 357. Flow of patients and study protocol are depicted in the flowchart [Figure 1]. The number of sputum AFB-positive samples was 120 in spot (S1), 110 in extra-spot (S2), and 119 in morning (M) sample. The total number of smear-positive pulmonary TB cases in the study was 123 considering the results of all three samples. The number of smear-positive pulmonary TB patients diagnosed on 1-day (S1 and S2) protocol was 120. The number of new smear-positive cases detected in morning samples which were smear-negative in 1-day protocol were only 2, that is, 1-day protocol missed 1.6% of cases. Whereas 3 of the 18 dropped out patients were sputum-positive for AFB in the first spot sample. The conventional 2-day protocol diagnosed 119 (96.75%), while the experimental 1-day protocol diagnosed 120 (97.56%) of all smear-positive TB patients [Table 1]. Chi-square test was applied for comparison between the two protocols [Table 2]. *P* - value was 0.7, which implies that there is no statistical

Table 3: Diagnostic validity of 1-day protocol against standard 2-day protocol

Protocol	2-Day protocol (D2)		Total	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
1-Day protocol (D1)				98.32	100	100	99.17
Positive	117	0	117				
Negative	2	238	240				
Total	119	238	357				

PPV: Positive predictive value; NPV: Negative predictive value

difference between these two diagnostic protocols. Gold standard investigation for diagnosis of pulmonary TB is sputum culture, but in program setting 2-day spot-morning method is considered as standard approach. When the new 1-day method was compared against 2-day method as gold standard [Table 3], it had sensitivity 98.32%, specificity 100%, positive predictive value 100%, and negative predictive value 99.17%.

Discussion

Till date, WHO recommends sputum microscopy for diagnosis of pulmonary TB. Due to low sensitivity of this investigation, the number of sputum samples required to be tested to achieve satisfactory diagnostic yield was a matter of intense research.[8] Many countries adopted a spot-morning-spot sputum sample strategies in national TB control programmes. After many studies including those from India, it was stated in WHO 2007 document that approximately 85.8% of patients were diagnosed with first sputum sample. Incremental yield of second sample was 11.9% and that of third sample was only 3.1%.[8,9] WHO recommended that examination of two sputum samples may suffice in countries with established quality control measures for laboratories. The diagnostic yield of morning sputum sample was higher compared to spot samples, and hence RNTCP India adopted Spot-Morning sputum sample strategy.[8] The advantages and disadvantages of three schemes, that is, "Spot-Morning-Spot," "Spot-Morning," and "Spot-ExtraSpot" are discussed in Table 4. The "END TB Strategy" proposed by WHO with a goal to end the "global tuberculosis epidemic" by the year 2035 has set the targets of reduction of TB deaths by 95% and reduction of TB incidence rate by 90% compared to 2015. Financial protection to TB-affected families is a new target of "END TB Strategy" so that "No TB affected families should face catastrophic financial loss due to TB by 2020.[10] With the current RNTCP protocol, patients have to come to the health facility on two consecutive days for sputum sample submission. Almost always the patients are accompanied by an adult attendant during these hospital visits. The cost of the diagnostic process for the patient includes transport, accommodation, food for at least two persons, and clinic cost whenever applicable which may include laboratory investigations, X-rays, and so on. According to a study conducted in Nepal and Yemen, this cost accounts for approximately 1 week's per capita income in these countries.[11] Excluding the clinic cost, the remaining expenditure gets doubled for a 2-day protocol compared to 1-day protocol. More importantly, there is contributory

Table 4: Comparison of different diagnostic strategies

Schemes	Advantages	Disadvantages
Spot-Morning-Spot	High diagnostic yield	High laboratory cost -2-day hospital visits -Financial loss to patient -Patient dropout -Delay in starting treatment
Spot-Morning	-No significant loss in diagnostic yield -Saves laboratory cost	-Still 2-day hospital visit -Financial loss to patient -Patient dropout -Delay in starting treatment
Spot-ExtraSpot	-No significant loss in diagnostic yield (as proven in this study also) -Saves laboratory cost -Only 1-day hospital visit -No financial loss to patient -No patient dropout -Treatment starts same day	-Morning sample has better diagnostic yield than extra-spot sample

When adjusted for the patients dropping out of submitting morning sputum samples, there is no significant difference in the number of patients with TB detected between morning and extra spot sample

hidden cost related to loss of income due to these hospital visits. These are expected to be the major factors responsible for patients dropping out of the diagnostic process.[12-14] The anticipated number of TB cases worldwide in 2014 was 9.6 million, but only 6 million cases were reported to WHO, that is, only 64% of the anticipated number of cases were reported; 36% of cases were either undiagnosed or not reported.[15] This reflects a gap in reporting and access to healthcare. Ten countries account for 74% or 2.4 millions missed TB cases globally and India tops the list contributing to 27% of these cases.[16] The longer it takes to diagnose and start treatment, an undiagnosed sputum-positive pulmonary TB patient keeps on transmitting the infective organism to others during transport, repeated hospital visits, and during the stay in various places of accommodation. If the diagnostic process can be completed in 1 day and treatment started on the same day itself, these issues of providing financial protection to patients, reducing the dropout rates from diagnostic process or finding the missed cases of TB, and breaking the chain of infection transmission can be addressed.

In this study, the single-day approach was found to have similar diagnostic accuracy as the current RNTCP 2-day protocol for diagnosis of TB. Similar studies done in the past with their

Table 5: Findings of earlier studies on 1-day smear microscopy method

Author	Place of study	Year	*N*	Results
Anyim *et al.*[20]	Nigeria	2006	752	There was no significant difference in the diagnostic values between the 2-day three sputum sample AFB microscopy and 1-day two sputum sample AFB microscopy.
Cambanis *et al.*[19]	Ethiopia	2006	243	There is no statistical difference between the same-day method and standard 2-day three sputum method for diagnosis of TB.
Hirao *et al.*[18]	Nigeria	2007	224	It could be possible to diagnose TB in a single day by examining two spot specimen.
Rawat *et al.*[17]	India	2010	513	2-Day protocol did not show statistically significant difference in performance compared with 1-day protocol.
Myneedu *et al.*[25]	India	2011	330	Sensitivity of the standard method and same-day method was 58.25% and 40.07%, respectively, whereas specificity was similar in both, i.e., 99.55%.
Miremba *et al.*[21]	Uganda	2012	229	Sensitivity of both the frontloading and standard schemes was 91.1% while their specificity was 86.2% and 91.7%, respectively. There was excellent agreement between the diagnostic capacity of the two methods (P=0.47).
Nayak *et al.*[24]	India	2013	2551	Same-day microscopy method missed 17% smear-positive cases and did not increase the proportion of suspects providing second sample.
Chandra *et al.*[22]	India	2014	1537	Diagnosis of lung TB is possible with two spot sputum samples with modified ZN staining.
Chandra *et al.*[23]	India	2016	3186	Sputum smear positivity was similar for both standard and same-day method for diagnosis of pulmonary TB.
This study	India	2016	375	1-Day method has same diagnostic efficacy as standard 2-day method (P-value 0.7).

N: Number of study participants; AFB: Acid-fast bacillus; TB: Tuberculosis; ZN: Ziehl-Neelsen

primary results are given in Table 5.[17-25] Seven of the nine studies had results similar to our study and recommended 1-day approach for diagnosis of pulmonary TB.

Conclusion

One-day protocol for diagnosis of pulmonary TB has equal diagnostic efficacy as standard 2-day protocol and it can be adopted as the standard diagnostic approach under RNTCP after multicentric large-scale studies.

Limitations of the study

The limitations of the study are as follows:

1. Sample size was small
2. It was not a multicentric study
3. Smear-positive cases could not be confirmed by culture.

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RNTCP, India.

Conflicts of interest

There are no conflicts of interest.

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