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Sputum Induction for the Diagnosis of Sputum Negative Pulmonary Tuberculosis: A Comparative, Randomised Study

Dr. Ajay Upadhyay[1], Dr. Kamendra Singh Pawar[2*]
[1]Assistant Professor, Dept. of TB and Chest, Government Medical College, Vidisha (MP), India
[2]Ex Senior Resident, Dept. of Pulmonary Medicine, All India Institute of Medical Sciences, Bhopal (MP), India

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***Corresponding author**
Dr. Kamendra Singh Pawar

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Abstract: With the rapid emergence of drug resistant bacilli, it has become important to get bacteriological confirmation of pulmonary TB in sputum smear negative patients. Sputum induction is simple and non-invasive, and may precludes the need for bronchoscopy. A prospective study was conducted among patients with smear-negative pulmonary TB with an objective to collect adequate sample of sputum with induction of sputum and compare sputum induction between nebulized N-acetyl cysteine (NAC), 0.9% normal saline (NS), and 3% hypertonic saline (HS). The consecutive 150 patients were taken fulfilling eligibility criteria and randomised in three groups and received nebulised 3% hypertonic saline, N-acetyl cysteine and 0.9% normal saline. There were 92(61.3%) male and 58 (38.6%) female in study population. The mean age of study group was 39.7 years (range 18-75). Sputum induction was successful in 125(83.3%) patients. Overall, 24.6% (n=37) patients were found positive on smear examination after sputum induction. Induction with 3% HS (n=50) was successful in 94% (n=47) patients while NAC and 0.9% NS induced sputum in 84% (n=42) and 72% (n=36) patients respectively. The percentage of smear positivity among successfully induced sputum was highest in 3% HS group (n=20/47, 42.5%). In conclusion, all the three agents can be used for sputum induction in sputum smear negative pulmonary TB but efficacy of 3% HS is better than other two agents.

Key words: Tuberculosis, sputum induction agents, induced sputum, India

INTRODUCTION

Tuberculosis (TB) is known to be an ancient disease, with skeletal disease being found in Egyptian mummies even dating back c. 3000 BC [1].

Globally, TB is the ninth leading cause of death [2]. In 2016, there were an estimated 1.3 million TB deaths among HIV-negative people [2]. There were an estimated 10.4 million new TB cases in 2016 and among these, 56% were from five countries namely; China, India, Indonesia, the Philippines and Pakistan [2].

Early identification of persons with TB remains the most effective way of preventing TB transmission. Good numbers of pulmonary TB suspects either do not produce adequate sputum spontaneously or are smear negative for acid fast bacilli (AFB) [3]. With the rapid emergence of drug resistant bacilli, it has become important to get bacteriological confirmation of pulmonary TB in sputum smear negative patients [4]. The diagnostic yield of induced sputum is comparable to bronchoscopy in patients unable to expectorate adequate sputum or spontaneous sputum smear negative in evaluation of suspected pulmonary TB and induced sputum has been advocated as a useful tool [3-4].

Sputum induction has been practised for last many years in evaluation of respiratory diseases [5]. In high TB burden, low resource countries, induced sputum can increase diagnostic yield [5]. Sputum induction is simple, safe, non-invasive and cost effective and can preclude the need for bronchoscopy [3-5].

In view of a limited systematic studies of supervised induced sputum in high TB burden countries, a prospective study was conducted among patients with smear-negative pulmonary TB with an objective to collect adequate sample of sputum with induction of sputum in subjects who do not produce adequate sputum spontaneously and compare sputum induction between nebulized N-acetyl cysteine (NAC), 0.9% normal saline (NS), and 3% hypertonic saline (HS).

MATERIALS AND METHODS

This prospective study was conducted at Department of Respiratory Medicine, New Medical College, Kota (Rajasthan) during Aug 2014 to July 2015. The consecutive 150 patients were taken fulfilling eligibility criteria and randomised in three groups irrespective of sex. Informed written consent was obtained from patients. The study was approved by Institutional Ethical Committee.

Patients presenting with cough of at-least 2 weeks with clinical and radiological picture consistent with active pulmonary tuberculosis with sputum either not producing or inadequate for examination (only saliva or sputum quantity <2 ml) and found to be sputum smear negative for AFB on two samples were taken for study.

Patients with concurrent uncontrolled asthma or chronic obstructive pulmonary disease, active hemoptysis, recent eye surgery, unstable cardiovascular status were excluded. Patients already receiving anti-tuberculous therapy (ATT) and age <18 years were also excluded.

All patients were subjected to detailed clinical history, examination and haematological, biochemical investigation, chest X ray and voluntary HIV testing. Sputum analysis was done for qualitative assessment including gram and Ziehl- Neelsen (ZN) staining.

The present study was conducted with the aim to compare sputum induction in smear negative pulmonary TB patients who were unable to produce/expectorate adequate sputum with nebulized (a) 0.9% NS, (b) 3% HS, and (c) NAC. Patients were randomised to receive sputum induction agents as per study protocol in three groups (each with 50 in number).

Each patient was nebulized with ultrasonic nebulizer with selected sputum induction agent (10 ml) and two sputum samples were collected i.e. first nebulized spot sample and next day early morning sample. Based on level of hydration, sputum production may be delayed for half an hour to 24 hours later [6]. Hence, patient was instructed to collect next day early morning sputum sample too. A short description of the procedure was given to patients. The procedure was performed in a well-ventilated room and adequate safety measures were taken for the staff members who supervised the procedure. Before nebulization, patients were asked for repeated rinsing and gargling with saline till returned fluid was clear. During nebulisation, patients were asked to take deep breaths and cough vigorously, if failed for spontaneous coughing. Till adequate amount of sputum sample (minimal 2ml) or maximum allotted time period of 30 minutes has elapsed, nebulisation with selected induction agent was continued [6]. In case of respiratory discomfort , procedure was discontinued. The procedure was interrupted every 5–10 min, so that patient can expectorate sputum. The procedure was performed under supervision. Vigilant monitoring was done for development of adverse events. The induced sputum sample was collected in a sterile, calibrated sputum container and appropriately labelling was done. Adequate decontamination of nebulizer equipment was done with 2% glutaraldehyde.

The induced sputum samples were submitted to the microbiology laboratory for assessment of good quality sputum by Gram stain based on squamous cell and polymorph count [7]. The successful sputum induction was accepted if sputum induced was in agreement with good quality sputum. All the sputum specimens were examined for AFB by ZN staining in the designated laboratory.

STATISTICAL ANALYSIS

Data collected were entered in Microsoft excel 2010 worksheet in the form of master chart. Categorical variables were expressed in absolute numbers or percentages and continuous variables were expressed as mean±SD. The statistical analysis was performed using MaxStat Lite version (Version 3.60).

RESULT

The total number of study population was 150. There were 92(61.3%) male and 58 (38.6%) female. The mean age of study group was 39.7 years (range 18-75). The most common radiological finding was consolidation in 66% (n=99) patients followed by fibrosis (28%, n=42). Cavitation was seen in 15 (10%) patients.

Sputum induction was successful in 125(83.3%) patients. Induction with 3% HS (n=50) was successful in 94% (n=47) of patients while NAC and 0.9% NS induced sputum in 84% (n= 42) and 72% (n=36) patients respectively. In our study the efficacy of induction was maximum for 3% HS (Table 1). Overall, 24.6% (n=37) patients were found positive on smear examination after sputum induction.

The percentage of smear positivity among successfully induced sputum was highest in 3% HS group (n=20/47, 42.5%) (Table 2). In group of the 3% HS, overall 40% (n=20/50) were found to be smear positive after induction of sputum while NAC group showed 18% (n=9/50) positivity rates. The lowest smear positivity rate was found amongst 0.9% NS group (n=8/50, 16%) (Table 3). In our study the 1st spot sample in all the three groups was found more consistently positive as compared to next day early morning samples (table 4).

Table-1: Showing sputum induction proportions of each agent

Sputum induction agent group	Sputum induced	Sputum not induced	Total patient
3% HS	47 (94%)	3(6%)	50
NAC	42 (84%)	8(16%)	50
0.9% NS	36 (72%)	14(28%)	50

Table-2: Percentage of sputum positivity on successfully induced sputum

Sputum Induction Group	Successfully Induced Sputum	Smear Positive	Percentage
3% HS (n=50)	47	20	42.5%
NAC (n=50)	42	9	21.4%
0.9% NS (n=50)	36	8	22.2%

Table-3: Smear microscopy results on induced sputum

Sputum Induction Group	Smear Positive on Induced Sputum	Smear Negative on Induced Sputum
3% HS (n=50)	20(40%)	30(60%)
NAC (n=50)	9(18%)	41(82%)
0.9% NS (n=50)	8(16%)	42(84%)

Table 4 Cumulative 1st and 2nd sample results of different agents

Sputum Induction Group	1st spot sample	2nd early morning sample	Total Positive	Total Negative
3% HS (n=50)	+ve	+ve	4(8%)	
	-ve	+ve	6(12%)	
	+ve	-ve	10(20%)	
			20 (40%	30
NAC (n=50)	+ve	+ve	2(4%)	
	-ve	+ve	2(4%)	
	+ve	-ve	5(10%)	
			9(18%)	41
0.9%NS (n=50)	+ve	+ve	2(4)%	
	-ve	+ve	2(4%)	
	+ve	-ve	4(8%)	
			8(16%)	42

DISCUSSION

Quality of the sputum invariably affects the laboratory test results for diagnosing pulmonary TB and the poor quality sputum may be responsible for missing TB diagnosis for all test i.e. microscopy, culture and PCR based tests [8]. In our study, sputum induction was successful in 125(83.3%) patients and 24.6% of patients were found positive on smear examination after sputum induction.

In an Indian study [9] sputum induction was successful in 95% of patients suspected of pulmonary TB and 32% were found smear positive following sputum induction. Another study [10] found smear AFB positivity in 76 cases (63.3%) on induced sputum. In study conducted by Gupta *et al* [11], in 97% patients, sputum induction was successful with 3% HS and among these successfully induced sputum samples 39.1% (n=38) were found positive on AFB staining.

In the present study, among 3% HS group, sputum was induced successfully in 94% of cases as compared to 72% of cases within the 0.9% NS group. Ansari *et al* [6] found sputum induction rates of 97.5% (n=39) in 3% HS group while in 0.9% NS group it were 50% (n=20) with overall sputum induction rates of 79.1% in pulmonary TB suspects. In their study, first spot sample were positive in 75% cases in 3% HS

group, while in 0.9% NS group, first spot sample was positive in only 25% cases [6]. Similarly in our study, first spot sample was more consistently positive in all three groups. So in our study, supervised sputum induction performed (induced spot sample) better than unsupervised early morning sample.

N-Acetylcysteine cleaves disulfide bonds in mucoprotein and helps in decreasing sputum viscosity that may aid in ease for expectoration of sputum [12]. A double-blind, randomised, placebo-controlled study [12], compared efficacy of nebulised NAC and 0.9% NS for obtaining good quality sputum found no significant trend towards NAC for improved quality of sputum sample. A study [13] conducted among smear negative pulmonary TB patients found 93.9% patient in nebulized NAC group (n=82) produced adequate sputum and sputum smear positivity rates among induced sputum noted were 33.7%. In our study, 84% patient induced sputum in NAC group and 21.4% sputum positivity rates were noted among successfully induced sputum in NAC group. In our study, both sputum induction and sputum positivity rates were better in NAC group as compared to 0.9% NS group.

In our study, overall 24.6% patients turned out to be smear positive after sputum induction while 3% HS performed better in terms of sputum induction and sputum positivity rates than 0.9% NS and NAC group. Here, NAC group performed slight better than 0.9% NS group. In a recent systematic review and meta-analysis [8], it was concluded that ‘‘Tuberculosis diagnoses were substantially increased by either pooled collection or by providing instruction on how to produce a sputum sample taken at any time of the day.’’

In our view, all the three agents can be used for sputum induction for the diagnosis of sputum negative pulmonary tuberculosis and in patients with inability to produce adequate quality sputum however preference should be given to 3% hypertonic saline.

CONCLUSSION

In conclusion, all the three agents can be used for sputum induction in sputum smear negative pulmonary TB but efficacy of 3% HS is better than other two agents.

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