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Original Article

Paediatrics Section

Evaluation of Induced Sputum against Gastric Juice Aspirate in the Diagnosis of Tuberculosis in Children: A Cross-sectional Study

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ABSTRACT

Introduction: Diagnosing Tuberculosis (TB) in children is difficult as they do not expectorate sputum on their own, and the sample is usually paucibacillary. Hence, alternative sampling methods like Gastric juice Aspiration (GA), which is the widely accepted method, and Induced Sputum (IS) collection, a more novel approach, are used. The IS method has several advantages, such as being less invasive, not requiring inpatient admission, causing less discomfort, and not necessitating overnight fasting, compared to the GA method.

Aim: To evaluate IS against GA for diagnosing TB using XpertMTB/RIF assay, as well as mycobacterial culture, in children aged between 2 and 15 years.

Materials and Methods: This cross-sectional study was conducted in the Department of Paediatrics at Christian Medical College and Hospital, Vellore, Tamil Nadu, India from June 2019 to March 2020, involving 138 children aged between 2 and 15 years who were being evaluated for TB. GA samples were collected after an overnight fast, and on the same day, atleast two hours later, IS samples were collected by trained staff. Both samples underwent mycobacterial smear and culture using the Mycobacteria Growth Indicator Tube (MGIT) method and Xpert MTB/RIF assay. Confirmation of pulmonary TB was based on atleast one of these tests being positive. The 'Wong-Baker' Visual Analogue Scale (VAS) was individually administered to each patient to compare the discomfort associated with GA and IS procedures. The differences in yield between IS and GA were tested for significance using the Two-sample test of proportions with a significance level set at 5%. McNemar's χ^2 test was employed to compare matched observations. The Mann-Whitney test was used for comparing continuous variables, and the Chi-Square test for categorical variables. Cohen's Kappa (κ) was used to assess interobserver agreement between the sampling methods using the different tests.

Results: Out of the 138 cases recruited with suspected pulmonary TB, the diagnosis was microbiologically confirmed in 13 cases (9.4%). The overall diagnostic yield was 12/138 (8.7%) for GA and 10/138 (7.2%) for IS. In children under 10 years, GA outperformed IS with all three cases being positive by GA and none by IS. For those aged 10 years and above, 10 children (100%) tested positive with IS, while nine children (90%) were positive with GA. According to the Wong-Baker VAS measuring discomfort during the procedure, IS was favoured over GA (p-value <0.0001).

Conclusion: IS performs similarly or better than GA in children over 10 years, while GA performs better than IS in children under 10 years of age. IS is reported to cause less discomfort than GA on the Wong-Baker VAS.

Keywords: Childhood tuberculosis, Diagnostic sampling, Gastric lavage, Paediatrics

INTRODUCTION

Diagnosing pulmonary TB in children is difficult as they do not expectorate sputum on their own, and the sample is usually paucibacillary [1]. Hence, alternative methods of sampling are employed [2]. The widely accepted method of sampling is GA [3]. In this method, the patient is kept fasting overnight, and GA is obtained through a nasogastric tube inserted into the stomach. A lavage can also be performed if the aspirate is insufficient. The collected sample is used for TB testing [4]. The IS method is a more novel approach in sampling [5]. In this method, children are given nebulised saline with oxygen for 15 minutes, administered chest percussion, and sputum is obtained by expectoration or via the throat or nasopharynx by suction using a sterile catheter. This technique is less invasive, does not require inpatient admission, causes less discomfort for the child, and does not require overnight fasting. However, it requires extra machinery, a skilled technician, and a special room dedicated for the purpose [6]. GA requires an overnight fast and has to be done early in the morning. It also requires the insertion of a nasogastric tube, which needs the expertise of a nurse and is an uncomfortable procedure. IS, on the other hand, does not require an overnight fast and can be done at any time of the day, causing less discomfort. GA is done only in a few centres across the country due to these logistic constraints. The benefits of IS as a procedure still outweigh the drawbacks, and if proven to be as effective as GA in obtaining a positive TB specimen, it has the potential to replace GA [7].

Although there has been literature published abroad that IS is an equally efficacious method of sampling as GA, there are only a few studies done in the Indian subcontinent [8]. Hence, to implement a new sampling technique, a methodical study is essential to establish relevance in the regional setting. Even though there are standard protocols for carrying out these sampling techniques, there can be a huge variation in the final technique that is actually implemented [6-8]. Hence, such a study is essential prior to extrapolating values done elsewhere to an Indian scenario. Thus, the aim of this study was to compare IS and GA in the diagnosis of TB in children.

MATERIALS AND METHODS

This cross-sectional study was conducted in the Department of Paediatrics at Christian Medical College and Hospital, Vellore, Tamil Nadu, India from June 2019 to March 2020 on children aged between 2 and 15 years being evaluated for TB. The study was approved by the Institutional Review Board (IRB) of the Christian Medical College, Vellore (IRB Min no. 11921) on June 6, 2019.

Inclusion criteria: All children with any one of the following criteria were included: Persistent cough and/or fever for more than two weeks, weight loss exceeding 5% over three months, no weight gain in the last three months, history of contact with a patient with any

form of active TB in the last two years, abnormal chest radiograph, a positive Mantoux test and being evaluated for TB [9].

Exclusion criteria: Children admitted to the intensive care unit and those already on any antituberculous drug were excluded from the study.

Study Procedure

GA was collected after an overnight fast, and on the same day, atleast two hours later, IS samples were collected by trained staff. Mycobacterial smear and culture using the MGIT method [10] and Xpert MTB/RIF assay [11,12] were performed on both these samples. Confirmation of pulmonary TB was based on atleast one of these tests being positive. The 'Wong-Baker' VAS was individually administered to each patient to compare the discomfort associated with GA and IS. A maximum allowable difference in diagnostic yield for IS to be considered non inferior to gastric juice aspirate was assumed to be 5%.

Due to the Coronavirus Disease-2019 (COVID-19) pandemic, the IS procedure could not be carried out, leading to a curtailed sample collection of a total of 138 children.

Diagnostic yield was calculated in two categories:

1. Crude yield: Crude yield is defined as the number of *Mycobacterium tuberculosis* positive cases divided by the total number of patients investigated for each category of the sample. Crude yield was calculated for:

a) XpertMTB/RIF assay:
   - Number of positive tests from the XpertMTB/RIF assay in GA samples divided by the total number of GA samples tested with the XpertMTB/RIF assay.
   - Number of positive tests from the XpertMTB/RIF assay in IS samples divided by the total number of IS samples tested with the XpertMTB/RIF assay.

b) MGIT culture:
   - Number of positive tests from the MGIT in GA samples divided by the total number of GA samples tested with the MGIT.
   - Number of positive tests from the MGIT in IS samples divided by the total number of IS samples tested with the MGIT.

c) Combination of the two tests (MGIT or XpertMTB/RIF assay):
   - Total number of cases positive from MGIT and XpertMTB/RIF in GA samples divided by the total number of GA samples tested for both the XpertMTB/RIF assay and MGIT.
   - Total number of cases positive from MGIT and XpertMTB/RIF assay in IS samples divided by the total number of IS samples tested for both XpertMTB/RIF and MGIT.

2. Differences in yield:
   - Number of patients positive on XpertMTB/RIF assay or MGIT on IS divided by the number of patients positive on either XpertMTB/RIF assay or MGIT on any sample.
   - Number of patients positive on XpertMTB/RIF assay or MGIT on GA divided by the number of patients positive on either XpertMTB/RIF assay or MGIT on any sample.

STATISTICAL ANALYSIS

The difference in yield can be calculated by subtracting these values obtained as percentages. Diagnostic yield was reported using proportions and 95% confidence intervals. Differences in yield between IS and GA were tested for significance using the two-sample test of proportions. The level of significance was set at 5%. The McNemar's χ^2 test was used to compare matched observations. The Mann-Whitney test was used to compare continuous variables, and the Chi-square test was used for categorical variables. The Cohen Kappa (κ) was utilised to compare interobserver agreement between the sampling methods using different tests. Cohen suggested that the Kappa result be interpreted as follows: values ≤0 indicate no agreement, 0.01-0.20 suggest none to slight agreement, 0.21-0.40 indicate fair agreement, 0.41-0.60 suggest moderate agreement, 0.61-0.80 indicate substantial agreement, and 0.81-1.00 suggest almost perfect agreement [13]. The Wilcoxon signed-rank test was used to compare the results of the 'Wong-Baker VAS' [14]. The data were entered in Microsoft Excel and analysed using Statistical Package for Social Sciences (SPSS) statistical software version 26.0.

RESULTS

Thirteen (9.4%) out of the 138 children recruited with suspected TB had microbiologically confirmed pulmonary TB. The overall diagnostic yield by GA was 12/138 (8.7%), while that for IS was 10/138 (7.2%) [Table/Fig-1], showing a 1.5% difference in diagnostic yield [Table/Fig-2].

1. XpertMTB/Rif assay	Positive (n=13)	Negative (n=125)	Total (n=138)	Crude yield*
a. Gastric juice aspirate				6.5% (3.4-11.9)
GJ+	9	0	9	
GJ-	4	125	129	
b. Induced Sputum (IS)				6.5% (3.4-11.9)
IS+	9	0	9	
IS-	4	125	129	
2. MGIT	**Positive (n=13)**	**Negative (n=125)**	**Total (n=138)**	**Crude yield***
Gastric juice aspirate				6.5% (3.4-11.9)
GJ+	9	0	9	
GJ-	4	125	129	
a. Induced Sputum (IS)				4.3% (2-9.1)
IS+	6	0	6	
IS-	7	125	132	
3. Both XpertMTB/ RIF assay and MGIT	**Positive (n=13)**	**Negative (n=125)**	**Total (n=138)**	**Crude yield***
Gastric juice aspirate				8.7% (5-14.5)
GJ+	12	0	12	
GJ-	1	125	126	
Induced Sputum (IS)				7.2% (3.9-12.8)
IS+	10	0	10	
IS-	3	125	128	

[Table/Fig-1]: Crude yield for GA and IS samples.
*Crude yield reported using proportions and 95% confidence interval

Specimen	n/N	Yield		Specimen	n/N	Yield	Yield difference*
1. XpertMTB/RIF assay							
GA	9/13	69% (38.6, 90.9)	Vs.	IS	9/13	69% (38.6, 90.9)	0% (0-3.7)
2. MGIT							
GA	9/13	69% (38.6, 90.9)	Vs.	IS	6/13	46% (19.2, 74.9)	23% (15.8-32.1)
3. XpertMTB/RIF assay or MGIT							
Specimen	n/N	Yield		Specimen	n/N	Yield	Yield difference*
GA	12/13	92.3% (64.0, 99.8)	Vs.	IS	10/13	76.9% (49.7, 91.8)	15.4% (10.1-24.4)

[Table/Fig-2]: Differences in yield between GA Vs. IS samples.
n: Number of positive samples obtained by each method; N: Total number of positive samples by GA or IS; *Yield difference reported using two test proportions and 95% confidence intervals

With the XpertMTB/RIF assay alone, both GA and IS had the same diagnostic yield of 9/138 (6.5%). Using the MGIT alone, GA had a superior yield with 9/138 (6.5%), compared to IS with

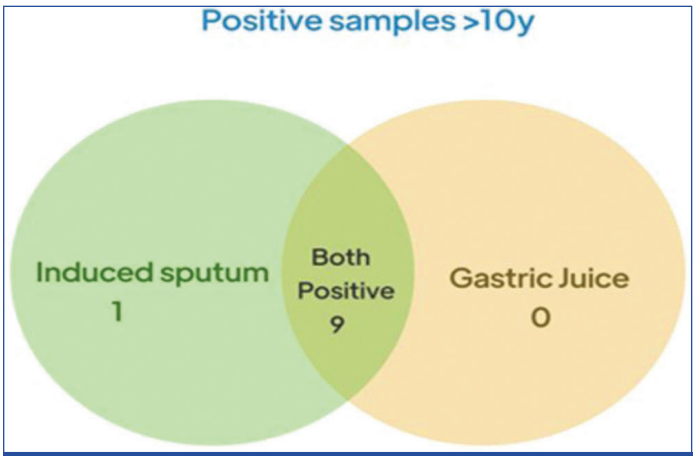
6/138 (4.3%), representing a 2.2% difference in yield. The Cohen's Kappa (κ) between GA and IS was 0.80, indicating substantial agreement [Table/Fig-3], suggesting that the results obtained by both sampling methods were largely similar. The Cohen Kappa (κ) was used to compare interobserver agreement between the sampling methods using different tests. In age-stratified analysis, in children <10 years, all the positives were obtained only by GA (100%), none by IS. In those >10 years, it was 90% with GA and 100% with IS. Out of the 13 positive subjects, 10 of the positive IS samples were from children above 10 years of age [Table/Fig-4,5]. Using the Wong-Baker VAS to assess discomfort associated with the procedures, GA had a median score of eight, while IS had a median score of 2, suggesting that IS was associated with significantly lower levels of discomfort compared to GA (p-value <0.0001) [Table/Fig-6].

	Both XpertMTB/Rif assay and MGIT			% of Agreement	Cohen's Kappa (κ)*
	GA+	GA-	Total		
IS+	9	1	10	97.1%	0.80
IS-	3	125	128		
Total	12	126	138		

[Table/Fig-3]: Percentage of agreement between GA and IS.

Age	Frequency (N=138)	Gastric juice aspirate positive	Induced Sputum (IS) positive	p-value
Less than 10 years	89 (64.5%)	3	0	<0.001*
Above 10 years	49 (35.5%)	9	10	

[Table/Fig-4]: Positive samples according to age group.
*Chi-squared test applied with one degree of freedom and a significance level of 0.05



[Table/Fig-5]: Positive samples in children >10 years of age.

Pain scale	GA (%)	IS (%)	p-value
0	5 (3.62)	62 (44.93)	<0.0001*
2	8 (5.80)	23 (16.67)	
4	17 (12.32)	17 (12.32)	
6	26 (18.84)	15 (10.87)	
8	30 (21.74)	14 (10.14)	
10	52 (37.68)	7 (5.07)	
Mean±SD	**7.2±2.9**	**2.8±3.2**	
Median (IQR)	**8 (6, 10)**	**2 (0, 6)**	

[Table/Fig-6]: Shows the pain scale between GA and IS.
*Wilcoxon signed-rank test applied

DISCUSSION

The current study aimed to compare the effectiveness of IS and GA for diagnosing TB in the paediatric age group. The effectiveness and comfort of the procedures were evaluated. The results indicated that IS caused less discomfort on the Wong-Baker VAS and that the overall diagnostic yield by GA (8.7%) was superior to IS (7.2%). Literature has shown varying results, with some favouring IS and others favouring GA. A study conducted in South Africa by Bunyasi EW et al., on 1,020 children with suspected TB found that 1.2% of IS samples tested positive, while 1.8% of GA samples tested positive using either the XpertMTB/RIF assay or MGIT. Therefore, they concluded that there was no significant difference in the diagnostic yield between the two sampling methods to justify choosing one over the other [15]. Singal KK et al., in a study conducted in India, sent a total of 176 samples (2 GA and 2 IS from each patient) from 44 patients. The smear positivity rates from IS and GA were 12.5% and 7.95%, respectively. The culture positivity rates from IS and GA were 3.4% and 0%, respectively. The smear positivity and culture positivity of IS were higher than GA in children with suspected pulmonary TB [12].

A study conducted in Spain by Ruiz Jiménez M et al., on 22 children with suspected TB identified 47.1% as positive with GA compared to 41.2% with IS. The study concluded that IS is a safe and well-tolerated technique that can be successfully performed even on infants, and it can be used as a complementary tool to increase the diagnostic yield of TB [8]. Hatherill M et al., published a study in South Africa in 2008, which showed that the crude yield of *Mycobacterium tuberculosis* was 5.8% and by GA was 6.8%, from a total of 194 cases [16]. Zar HJ et al., conducted a study on 250 children aged one month to five years and found that samples from IS and GA were positive in 87% and 65% of children, respectively, with a difference in yield of 5.6% (1.4-9.8%), p-value=0.018. The yield from one sample from IS was similar to that from three gastric lavages (p-value=1.0). All sputum induction procedures were well tolerated, and minor side-effects increased, such as coughing, epistaxis, vomiting, or wheezing. They found that IS is preferable to GA for the diagnosis of pulmonary TB in both HIV-infected and HIV-uninfected infants and children [17]. Beig FK et al., in a study conducted in India on 55 children suspected to have TB in 2011, showed a cumulative yield of 81.8% for IS and 45.5% for GA on the first specimens tested on smear and TB culture. The culture positivity for *Mycobacterium tuberculosis* was better with IS than GA, and the difference was statistically significant (p-value <0.05) [18].

In the present study that GA performed better than IS in children under 10 years, while IS performed better in children over 10 years. It would be prudent to use GA in younger children and IS in older children without compromising on the mycobacterial yield to make a definitive diagnosis of TB. There are a few studies that have objectively quantified and compared the degree of discomfort associated with IS and GA [19,20]. Children in the present study rated IS much better than GA on the VAS, which was also statistically significant (p-value <0.0001). Ronchetti K et al., assessed the tolerance associated with IS in 124 children (6 months to 18 years) with cystic fibrosis. The objective tolerance of the procedure was high, as reported by the parents and therapists, with 14% reporting mild side-effects [20]. These findings were similar to the present study, which showed good tolerability with IS. The diagnosis of confirmed paediatric pulmonary TB among suspects was lower than the incidence reported in various studies conducted in India and abroad. A comparison of yield between GA and IS from previous studies has been described in [Table/Fig-7] [8,12,15,17,21].

Limitation(s)

A limitation of present study was the small sample size. The sample size calculated was 220; however, only 138 samples could be recruited as the study had to be halted because IS was not permitted during the COVID-19 pandemic. Despite this limitation, authors were still able to demonstrate the comparative tolerance of IS and GA, in addition to the yield of microbiologically confirmed TB in the two groups. Therefore, future studies with a larger sample size would be beneficial in drawing further conclusions and helping

Study name, publication year	No. of children	Age group	Micro-confirmed pulmonary TB (%)	Yield							
				Overall		Smear		NAAT		Culture	
				IS (%)	GA (%)	IS (%)	GA (%)	IS (%)	GA (%)	IS (%)	GA (%)
Present study, 2024	138	2 y-15 y	9.4	7.2	8.7	-	-	6.5	6.5	4.3	6.5
Mukherjee A et al., India, 2013 [21]	433	6 m-15 y	37.7	-	-	5.7	10.4	-	-	17.9	32.5
Ruiz Jiménez M et al., Spain, 2013 [8]	22	1 m-14 y	58.8	41.2	47.1	3.9	5.9	29.4	16.7	25.5	33.3
Bunyasi EW et al., S. Africa, 2015 [15]	1020	4 m- 4 y	-	1.6	1.7	-	-	0.6	0.3	1.5	1.5
Singhal KK et al., India, 2014 [12]	44	1 m-12 y	15.9	-	-	12.5	7.95	-	-	3.4	0
Zar HJ et al., S. Africa, 2005 [17]	138	1 m-5 y	25	16	8	8	3	-	-	15	7.6

[Table/Fig-7]: Comparison of yield between GA and IS from prior studies [8,12,15,17,21].
M: Months; Y: Years; NAAT: Nucleic acid amplification test

clinicians choose the appropriate sampling modality based on factors such as age, tolerance, and diagnostic yield.

CONCLUSION(S)

Overall, the yield was better with GA compared to IS. However, in older children (>10 years), IS had better yield and showed better tolerability and less discomfort, as compared to GA. Therefore, it is suggested to use IS in children above 10 years of age and GA for children below 10 years of age.

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