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A study to evaluate the significance of Mantoux test investigated for tuberculosis in a tertiary care teaching hospital of India

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ABSTRACT

Background: Tuberculosis (TB) is a serious illness that mainly affects the lungs. The Mantoux tuberculin skin test (TST) is one method of determining whether a person is infected with *Mycobacterium tuberculosis*. Reliable administration and reading of the TST requires standardization of procedures, training, supervision, and practice. **Aims and Objectives:** The objective was to determine the sensitivity and specificity of Mantoux test in pediatric patients for the diagnosis of TB. It also assists to study various presentations of TB in Mantoux test-positive patients. **Materials and Methods:** From August 2022 to January 2023, a single tertiary care facility named Saraswathi Institute of Medical Sciences, Hapur hosted this observational study after approval from the Institutional Ethical Committee. Participants in the trial included all children up to 15 years of age who has received Bacillus Calmette-Guérin at birth, were suspected of having TB and had been referred to a pediatric TB clinic. TST by 5 Tuberculin Unit Purified Protein Derivative-Standard was used to see induration of various sizes. The sensitivity, specificity, positive predictive value, negative predictive value and other metrics were calculated during the study by statistical software. **Results:** Out of 480 patients 36.87% (n = 177) had TB with TST cut off ≥ 15 mm indurations, while 169 patients had no induration. Most common age group affected was 5–10 years (48.59%) followed by 0–5 years (30.51%) and 10–15 years (20.90%) with male: female ratio = 1.2:1. Most common etiology for TST positive patients was pulmonary TB (PTB) (29.30%), extra PTB (50.10%), disseminated TB (12.90%) and latent TB (07.70%). The sensitivity of the test was 95.857% with 95% confidence interval (91.64–98.31%), specificity was 95.176% (92.16–97.29%). Its positive and negative predictive values were 91.525% and 97.689% respectively. **Conclusion:** TB can be diagnosed with the Mantoux test because of its high sensitivity and specificity but it should be explained carefully to avoid inaccurate interpretations.

Key words: Mantoux test; Indurations; Sensitivity; Specificity

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INTRODUCTION

Tuberculosis (TB) is one of India's major public health problems. According to the World Health Organization (WHO), India has the world's largest TB epidemic.[1] Mantoux test, also known as the Mendel-Mantoux test, tuberculin sensitivity test, Pirquet test or PPD test for pure protein derivative, is a method for detecting TB and diagnosing disease.[2] Following injection of a tuberculin purified protein derivative (PPD), known as a tuberculin skin test (TST), the body develops a cellular immune response in reaction to current or prior TB infection and prior Bacillus Calmette-Guérin (BCG) vaccination. This immune response can be assessed through measuring dermal induration. This aids in the differential diagnosis of TB among children and to decide about administration of chemoprophylaxis.

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The usefulness of the test lies not only on proper technique of administering a standard dose of a standard tuberculin and reading of the reactions by trained personnel but also in its careful interpretation. However, there is no clear understanding among some of the medical practitioners and health workers regarding the performance and interpretation of the test. However, various factors both in the host and inherent in the test lower both its specificity and sensitivity.

As a result, its administration to any group of patients usually produces a wide range of outcomes, ranging from the presence of a reaction in children who are not infected to the complete absence of a reaction in certain children who have been diagnosed with TB disease. The test has a poor positive predictive value for the current active disease.[3] Some persons may react to the TST even though they are not infected with *Mycobacterium tuberculosis* (MTB).

According to a study, 2% error in measurement reduces the accuracy of Mantoux test by 25% and the impact exceeds 50% for 5% error. Other significant confounding elements include the use of various techniques for estimating induration size, the variability in reading test results over time and the potency of the PPD utilized in the test.[4] The Mantoux test is one of the important supportive tests for diagnosis of TB in the pediatric population and variability in the test results may lead to a dilemma in the diagnosis of childhood TB.

Thus, we had commenced this study to determine the sensitivity and specificity of Mantoux test`.

Aims and objectives

1. Our main objective was to analyze the sensitivity and specificity of TST in children to aid in the diagnosis of TB.
2. Our other objective was to researching different TB manifestations in people with positive Mantoux tests that will contribute knowledge in this field.

MATERIALS AND METHODS

Study design

This descriptive observational study was conducted between August 2022 and January 2023 in the Pediatrics Department of a tertiary care hospital with association of Pharmacology Department and Department of TB and Respiratory Diseases in northern India, after approval from the Ethics Committee of the Hospital.

Inclusion criteria

All children up to 15 years of age who had got BCG vaccine at birth, suspected case for TB and referred to pediatric TB clinic were enrolled in the study. Patients with positive contact history, low weight for age (<80% of expected/recent weight loss of 10%), persistant fever >2 weeks, persistant cough for >2 weeks or significant lymphadenopathy were included for study.

Exclusion criteria

We excluded children with severe malnutrition, recent viral illness, severe TB, abdominal typhoid, malignancy, children with recent vaccination (live attenuated vaccine), those in an immune-compromised state or patients already on treatment with anti TB therapy, prior Mantoux positivity (<1 year), non-consent of parent or guardian.

Ethical approval for the study was obtained from Ethical Committee of the Institution and informed consent was obtained from the parent or guardians of each children before recruitment.

An accurate history and clinical examinations were performed in all patients and clinical signs and symptoms such as fever (axillary temperature <37.5°C), skin rash (such as varicella, influenza, measles), cough, abdominal pain, vomiting, loss of appetite, loss of weight and lymph nodes were noted meticulously. Parents were asked about the history of household contacts with TB, exposure to elderly people with chronic cough or unexplained prolonged febrile illness.

Children who fulfilled the inclusion criteria were Mantoux tested by standard technique as recommended by WHO by trained staff or researcher under expert supervision. So that, the investigator's Mantoux readings were validated and to be highly reproducible, with a 98% degree of concordance.[5]

SPAN's tuberculin PPD was used in the study which was diluted to make a ready to use solution for performing Mantoux test. Source material is calibrated against batch RT23 manufactured by Staten's Serum Institute, Denmark. It is diluted with a buffer containing Tween-80 as stabilizer. The test was done by injecting 0.1 mL of tuberculin intradermally into the middle one third of the volar surface of right or preferably left forearm with 5 TU PPD-S using tuberculin syringe with 27-gauge needle without massaging or pressing the area.[6]

The diameter of the induration was measured in good light, along the transverse axis of forearm 48–72 hours after injection of the PPD with a plastic transparent meter ruler and also using the "ball point pen" technique of Sokal.[7] After injection, appearance of a pale wheal of 6–10 mm was taken as correct intradermal administration and an induration of 10 mm and above was considered positive.

The Mantoux reactions of the subjects were grouped into (modified from Egbagbe et al.[8]): (i) negative, induration 0–4 mm (ii) borderline, induration 5–9 mm (intermediate) (iii) positive, induration 10–14 mm (iv) moderately positive, induration 15–20 mm and (v) strongly positive, induration 21–30 mm. According to NTEP guidelines a test more than 15 mm was considered positive in all the patients.

The diagnosis of TB was based on either histopathological, clinical or bacteriological (smear/culture/polymerase chain reaction proven TB) grounds.[9]

A TB case was considered to be a child with MTB isolated from clinical specimens or with the presence of symptoms, signs and/or radiological images compatible with TB (thoracic computed tomography alternatively) and/or a positive TST and who responded clinically to antituberculous chemotherapy. Histopathologically, fine needle aspiration cytology suggestive of caseating granulomas consistent with TB. Again, bacteriological diagnosis was based on smear positive for acid fat fast bacilli and/or culture positive for MTB or a positive GeneXpert test.

Those who did not fulfill either clinical, histological or bacteriological diagnosis of TB were defined as not having TB as per WHO criteria.[9] A test more than 15 mm was considered positive with all patients. Data were collected on pre-tested proforma with clinical details.

Children with a positive Mantoux test were followed up and managed appropriately.

Statistical analysis

Data were entered into a computer and analyzed using SPSS and MedCalc statistical software. Data description was conveyed in absolute frequencies, using mean and standard deviation or median and range.

Data were evaluated for 95% confidence interval, P-value and standard error; sensitivity, specificity, likelihood ratios, positive and negative predictive values for all possible threshold values for calculation. Results were presented in percentages and frequencies were compared using Chi-square test. A $P<0.01$ was considered significant. The overall odds ratio of a positive response and disease was calculated.

RESULTS

We enrolled 520 patients, out of which 17 (03.27%) were excluded, 16 (03.08%) were lost to follow up and 7 (01.35%) discontinued interventions. Thus data analysis was done for 480 patients (Figure 1).

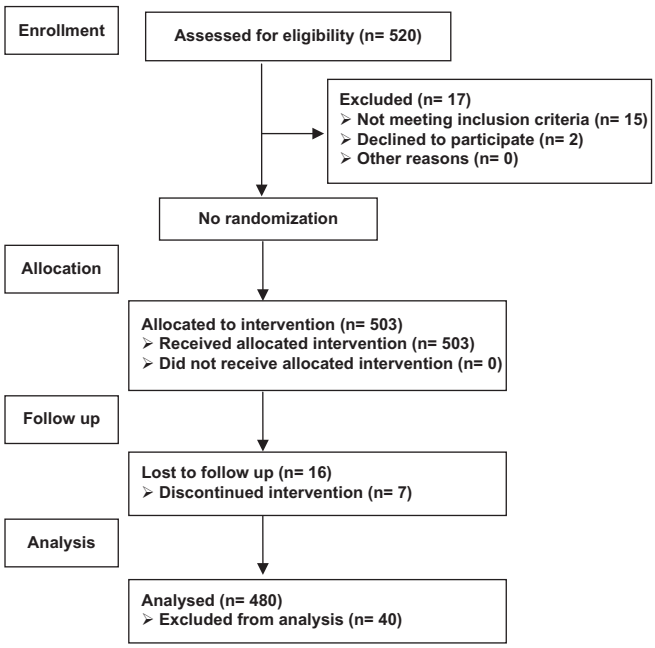

Figure 1: Study design analysis

Baseline characteristics of the study population showed that 33% patients were <5 years, 51.00% in between 5-10 years of age and 16.00% belong to the >10 years of age group population.

The active cases (n=177) had age distribution as, 54 (30.51%) belonged in 0–5 years of age group, 86 (48.59%) patients were in between 5 and 10 years age group while 37 (20.90%) patients pertained to the age of 10–15 years (Figure 2).

Mean age=7.01 years with S.D of 3.55 years.

The mean TST reading or induration in active cases was 16.24±6.7 mm.

There were 260 (54.17%) males and 220 (45.83%) females (male to female ratio=260: 220=1.18: 1=1.2: 1).

History of contact with sputum-positive cases were present in 10.30% of patients.

A comprehensive induration was noticeable in n=311(64.78%) patients and out of this 177 (36.87%) having TST cutoff as ≥15 mm were confirmed as positive cases. Again 96 patients had induration of ≥5 mm, 38 had in between 10-15 mm and 169 patients (35.21%) had no induration during testing.

A history of BCG immunization was recorded in 249 (51.86%) patients and BCG scar found in 64.00% of immunized patients.

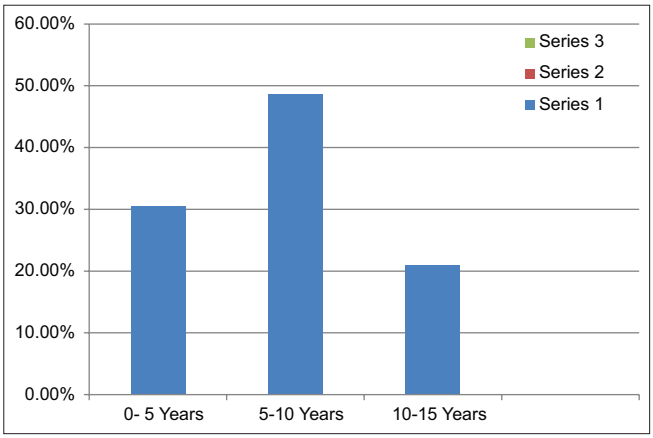

Figure 2: Significance of age groups in active tuberculosis cases

In the positive TB cases, pulmonary TB (PTB) was present in 52 (29.30%), extra-PTB (EPTB) was seen in 88 (50.10%), disseminated TB in 23 (12.90%) and latent TB or contact exposure was present in 14 (07.70%).

Despite the tuberculin test was being negative, diagnosis of TB was made on the basis of clinical evaluation, circumstantial evidence, radiology and other tests.

The diagnoses of TB was clinical in 127 (71.70%) patients, bacteriological in 28 (16.10%) and histopathological in 22 (12.60%) patients.

Tuberculin test was compared with gold standard bacteriological culture investigation to validate its results which was illustrated by using a conventional two-by-two (2×2) table (Table 1).

The sensitivity of tuberculin test was 95.857% where 95% C.I. (91.64–98.31%) were seen; while specificity was 95.176% with positive predictive value of 91.525% and negative predictive value 97.689% with high diagnostic accuracy (Table 2).

No remarkable adverse drug reactions were seen in any of the patients. But it was normally found that TST >20 mm usually associated with slight tenderness at the site of administration managed by standard treatment guidelines.

DISCUSSION

Mantoux test persists the widely used screening test to detect latent TB in developing countries like India. Using a cut-off of >15 mm induration, the study identified a prevalence of 36.88% positive Mantoux reaction. Our result near to other study finding of Lee et al., (2013) in Seoul, South Korea, which reported Mantoux prevalence of 36.50%.[10] The observed high prevalence of Mantoux test result in this study correlate that there is high latent TB prevalence and TB burden in this area of India. Also re-enforses the necessity for intensive and continuous screening methods and treatment of suspected TB infection as being critical to TB prevention and control in our population.

Table 1: Distribution of the patients as per sensitivity and specificity of the Mantoux test

Tuberculin test	Bacteriological culture		Total
	Positive	Negative	
Positive	162	15	177
Negative	7	296	303
Total	169	311	480

Table 2: To assess various statistical parameters of association between Mantoux test and bacteriological culture in the study population

Statistics	Value	95% Confidence interval
Test specificity	95.176%	92.16% - 97.29%
Test sensitivity	95.857%	91.64% -98.31%
PPV or positive predictive value	91.525%	86.82% -94.65%
NPV or negative predictive value	97.689%	95.34%- 98.86%
Likelihood ratio (LR) positive test	19.887	12.12–32.60
Likelihood ratio (LR) negative test	0.04	0.02–0.09

Sensitivity: Probability of being test positive when disease is present. Specificity: The ability of a test to correctly classify an individual as disease free is called the test's specificity. PPV: It is the probability (patient having disease when the test is positive), NPV: Defines probability of test (patient not having disease when test is negative). Positive and negative predictive values are directly related to the prevalence of the disease in the population; as the disease prevalence increases, the PPV value also increases

Interpretation of tuberculin reaction

The interpretation of the result, however, is often difficult with various workers using different induration sizes to indicate a positive reaction. TST persisted in widespread use, due to its low cost, simplicity of administration and interpretation. But, results of this test in BCG vaccinated children may have to be depicted with caution to avoid over-diagnosis of TB and unnecessary treatment with ATT.

The Tuberculin test is a diagnostic tool with high sensitivity and specificity for detecting TB infection where cellular immunity provides protection against infection.[11] The analysis of the test is complicated by cross-sensitivity induced by environmental mycobacteria or BCG- vaccination or atypical mycobacterial infection.[12] Not all reactions to tuberculin are inferable to infection with tubercle bacilli. A recent study in Madrid Spain done in children found that BCG given at birth does conflict with TST and may cause a false-positive TST result.[13]

The reactions with induration of <5 mm usually indicate lack of tuberculin sensitivity and absence of infection either with tubercle bacilli or environmental mycobacteria.[14] But patients suffering from severe degree of immune-suppression may also show induration in this range.

5 mm or more is positive in persons with recent contacts with a TB patient, HIV-positive case, patients with organ transplants, immune suppressed patients, persons with fibrotic or nodular changes on chest X-ray consistent with old healed TB or end stage renal disease.

Again 10 mm or more is positive in children <4 years of age or children and adolescents exposed to adults in high-risk categories; persons with high risk clinical conditions (like diabetes, prolonged corticosteroid therapy, leukemia, chronic malabsorption syndrome, low body weight etc.), injection drug users, recent arrivals from high prevalence countries, residents and employees of high risk congregate setting (e.g., nursing homes, hospitals, prisons), lab personnel.[15] We considered the Mantoux test to be positive for induration of ≥15 mm in BCG-vaccinated subjects.

TST ≥15 mm are unlikely to be due to previous BCG vaccination or exposure to environmental mycobacteria.[16] A study in Canada showed that Mantoux test induration cut-off point of 15 mm was able to eliminate the false positive BCG effects.[17] Normally, if Mantoux test is positive the patient should be treated with Antitubercular drugs to prevent development of overt disease. But as this test is dependent on many variables, that may alter its interpretation and result, there is a deadlock regarding which value of induration should be taken as significant.

Even when they are not infected with MTB, some people may react to the TST. The following are only a few examples of the potential reasons of these false-positive reactions: incorrect interpretation of the response, non-tuberculous mycobacterial infection, using the wrong antigen bottle of TST etc.[18] Since the test's specificity was inadequate, the majority of positive results in low risk people were false positive. Typically, a negative Mantoux result implies that the person has never been exposed to mycobacteria. A decreased capacity to respond to tuberculin or a false negative result, however, might occur from a number of causes.[19]

Skin anergy or inability to react to skin (fresh TB infection <10 weeks of exposure) test due to weakened immune system, extremely young age, long term TB (<6 months), fresh immunization against live virus (e.g. measles, small pox), viral diseases, devastating TB illness, incorrect TST administration or interpretation, inadequate dose or accidental subcutaneous injection can produce false negative results. The lack of prior sensitization, a false-negative result from a variety of causes or skin anergy brought by immune suppression can all contribute to the absence of cell-mediated immunity to tuberculin. The majority of the children with negative results did not suffer from MTB infection. A small percentage of infants with this infection who were otherwise healthy nonetheless test negative for PPD for unknown reasons.

There is a window of time between the moment of infection and the onset of CMI, ranging from 2 to 6 weeks, during which the Mantoux test would be negative. The PPD test typically yields negative results in patients with immunological deterioration, particularly in those with HIV and low CD_4 T-Cell counts. Negative results can be interpreted as either indicating that the individual has not been exposed to the TB bacteria or that the individual has been exposed but the exposure has not yet provided enough time for the body to respond to the skin test. Before 1 week, a repeat test is not advised since the tuberculin injection used for the initial test has a booster effect on the second dose. Eight weeks after Mycobacterium infection, also known as the "Window Period" the TST may become positive.[19] A Second Test is advised after eight weeks if the first TST was negative because infection cannot be ruled out before that time. We also analyzed the effects of various social and demographic variables such as age, sex and close contact with TB.

The majority of the active cases were in the age group between 5-10 years (48.59%) followed by 0–5 years (30.51%) and 10–15 years (20.90%) with male predominance. In one survey conducted by National TB Institute, Bangalore found resembling result with this study in respect of age and sex among the patients.[20] Outcome of TST in presence of close contact was not significant as seen by other study conducted in other parts of India.[21] Our study, had similar observations with high prevalence of Mantoux positivity among BCG vaccinated subjects that have been reported by workers in Africa as well.[22]

The most common etiology of Mantoux test positive patients was EPTB (50.10%), PTB (29.30%), disseminated TB (12.90%) and latent TB in 07.70% patients.

The sensitivity of the Mantoux test to detect active TB was 95.857% with CI of 95% (91.64–98.31%) while specificity was 95.176% with positive predictive value of 91.525% and negative predictive value of 97.689%.

In a study, in South India among healthy school children, the positive and negative predictive value for induration more than 10–15 mm at 24 h was estimated at 96.70% and 99.50% respectively closer to our study results.[23] In another study done by Oztwik et al., the tuberculin test

had a sensitivity of 94%, closer to our results but reported low specificity of 75%.[24] This study also revealed a positive diagnostic value of tuberculin test with its significant screening efficacy in accordance with another study by Lee et al.[25] Lee et al., had reported sensitivity of 94% with (95% CI, 87–98%), specificity 88% (95% CI, 74–96%), PPV 95% (95% CI, 88–98%) and NPV 86% (95% CI, 72–94%) supports our findings.

Limitations of the study

The limitation of the study was smaller study population. So more studies are needed on larger samples to highlight the importance of superiority of the Mantoux test as diagnostic tool.

CONCLUSION

It can be concluded from this study that Mantoux test can aid in early and more reliable diagnostic clue for pediatric TB; which can thereby facilitate early targeted treatment. In our population, the test had showed high sensitivity and specificity. This study paves way for large scale studies in this direction and in making of guidelines.

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Saborni Dey- Concept and design of study, manuscript preparation, data collection, statistically analyzed and interpreted, critical revision of the manuscript; **Vivek Tyagi & Nalluri Venkata Sai Charan -** Collected data, statistically analyzed and interpreted, review of the manuscript; **Siddarath Kumar -** Collected data, statistically analyzed and interpreted, critical revision of the manuscript, written text materials.

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