A PAIRED COMPARISON OF TUBERCULIN SKIN TEST RESULTS IN CHILDREN WITH CLINICAL MANIFESTATIONS OF TUBERCULOSIS USING 2 TU AND 5 TU TUBERCULINS

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ABSTRACT

Rationale: A paired comparison of reactivity to purified protein derivative 2 TU PPD RT-23 and 5 TU PPD-S in children with clinical manifestations of tuberculosis was done to assess if 2 TU PPD RT-23 can be used instead of 5 TU PPD-S in routine Mantoux testing in the country.
Objective: To determine the correlation of skin test reactivity to 2 TU PPD RT-23 and 5 TU PPD-S.
Study Design: Cross Sectional Study.
Methods: Two simultaneous skin tests using 2 TU PPD RT-23 and 5 TU PPD-S were performed. Each dose was randomly assigned in a blinded manner to the right or left forearm and read after 72 hours. Correlation between the size of induration obtained with 2 TU PPD RT-23 and with 5 TU PPD-S was done, as well as, correlation between tuberculin reactivity and age, gender, nutritional status, presence of BCG vaccination, exposure, and clinical manifestations. A p-value <0.05 was considered statistically significant.
Results: Sixty five patients were included in the study. The overall mean difference in paired reaction sizes for the two doses was -1.02 $\pm$ 2.8 mm (range of -11 to 3 mm). Using the present guidelines in the country to determine a positive tuberculin skin test, 27 (41.5 %) patients were positive when tested with 2 TU PPD RT-23 and 33 (50.8 %) patients were positive when tested with 5 TU PPD. The mean PPD size with 2 TU was 4.7 mm $\pm$ 6.1 mm compared to 5.8 mm $\pm$ 6.1 mm with 5 TU. PPD skin test reactivity with the two reagents was highly correlated (intraclass correlation 0.88; 95% CI 0.83-0.94). There was no significant association between age, gender, nutritional status, presence of BCG vaccination, TB exposure, and clinical manifestations to tuberculin reactivity.
Conclusion: Tuberculin skin test reactivity among children, who were with clinical manifestations of tuberculosis and tested with 2 TU PPD RT-23 and 5 TU PPD-S, were found to be comparable. Age, gender, nutritional status, presence of BCG vaccination, TB exposure, and clinical manifestations were not factors influencing the size of the PPD reaction. 2 TU PPD RT-23 can be used instead of 5 TU PPD-S in routine Mantoux testing.

INTRODUCTION

The tuberculin skin test is the most widely-used method to determine latent TB infection (LTBI), particularly, in individuals infected with M. tuberculosis (MTB), who do not have TB disease.[1] It is used in epidemiological surveys, in the clinical evaluation of patients with suspected active tuberculosis, and in assessing the need for preventive antituberculous drug therapy.

The basic principle behind the tuberculin test is the injection into the skin of a protein prepared from a culture of MTB, a tuberculin purified protein derivative. If the patient has been infected with MTB, a local, delayed-type hypersensitivity reaction will occur within days. The resultant induration can be assessed.[2]

The "optimal" dosage of tuberculin was determined in the 1940s and 1950s. Persons with and without histories of exposure to tuberculosis were tested with increasing doses of tuberculin and the cumulative proportions of reactors was calculated. From these studies it was concluded that 5 TU was the dose that gave the best balance between sensitivity and specificity.[3]

The American Thoracic Society (ATS) and the Center for Disease Control and Prevention (CDC) in the United States, endorsed the 5 TU PPD-S as the standard dose for tuberculin skin test in North America. Newly-manufactured batches of tuberculin are bioassayed and the standard test dose of a commercial PPD preparation was defined as the dose of the product that is biologically equivalent to that contained in 5 TU of PPD-S.[4]

PPD RT-23 is the most widely used tuberculin skin test in the world. The World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD) recommended the 2 TU PPD RT-23 as the standard dose for Mantoux tuberculin skin test surveys.[5] This is equivalent to two fifths of the concentration of antigen determined to be bioequivalent to 5 TU of PPD-S, which is the standard tuberculin preparation. Therefore, a dose of 0.1 ml of 2 TU PPD RT-23 is biologically equivalent to 0.1 ml of 5 TU PPD-S.

Using a 10 mm cut-off point for positive tuberculin reactivity, a simultaneous comparison regarding PPD reactivity between 2 TU PPD RT-23 and 5 TU PPD-S involving 202 health workers was done; they were found to be comparable.[6] As a rule of thumb, 0.1 ml of 2 TU PPD RT- 23 will have tuberculin reactivity similar to 0.1 ml of 5 TU PPD-S.[7]

There are many variables which may affect the tuberculin skin test interpretation and result. These include variation in tuberculin dose and formulation, experience and technique in performing the procedure, the effect of previous BCG vaccination, and subject's age, recent vaccination with live vaccines, and underlying immunosuppression.[8]

Among the different tuberculin skin tests, the Mantoux test using PPD 5 TU PPD is currently available and commonly used in the local setting. A cut-off size ≥ 10mm has a 99.7% sensitivity and 89.8% specificity, with culture as the reference standard.[9] Local studies have confirmed this cut-off to differentiate infected Filipino children from the uninfected.[10 11 12 13]

The 2 TU PPD RT-23 was previously utilized in the 1990s in the diagnosis of TB infection. The study of Rigor et. al. in 1988, however, showed that a significantly greater proportion of children with TB showed positive results with BCG than 2 TU PPD (z=0.512, p=0.006010).[14] Bonus et. al., on the same year, reported the sensitivity of 2 TU PPD among non-BCG recipients, who were diagnosed to have primary complex at 41%.[15]

Presently, the 2 TU PPD is being recommended by the Department of Health Task Force on Childhood Tuberculosis to be used as the test reagent for routine tuberculin skin testing in the Philippines. Through this study, a paired comparison of reactivity to purified protein derivative 2 TU PPD RT-23 and 5 TU tuberculin, among children with clinical manifestations of tuberculosis will be done to

assess if 2 TU PPD-RT 23 is comparable to that of 5 TU PPD.

MATERIALS AND METHODS

Definition of Terms

PPD RT-23 refers to a special batch of tuberculins prepared by Statens Serum Institut in Copenhagen in 1958 by agreement with UNICEF and the World Health Organization (WHO). This tuberculin batch with Tween 80 as a stabilizing agent, is used in surveys and is the most widely used tuberculin skin test in the world.[13]

PPD-S refers to the international standard of mammalian-type PPD tuberculin and prototype of the product used in the United States. The American Thoracic Society and the Center for Disease Control and Prevention in the US endorse the 5 TU PPD-S as the standard dose for tuberculin skin test in North America.[13]

Tuberculin Skin Test

A procedure where tuberculin is injected intradermally in the dorsal or volar aspect of the left forearm through special disposable 1 ml syringes, with gauge 26, 10mm long, disposable needles of short bevel. The procedure is read in mm, 3 days after administration by carefully palpating the largest transverse diameter of induration relative to the arm.

Tuberculosis in Children

a. Clinical Tuberculosis

A Child who has Tuberculosis has 3 or more of the following criteria:

1. (+) history of exposure to an adult/adolescent with active TB disease;
2. (+) Mantoux tuberculin test;
3. (+) signs and symptoms suggestive of TB (one or more of the following should be present):

3.1 cough/wheezing > 2 weeks; fever > 2 weeks;

3.2 painless cervical and/or other lymphadenopathy;

3.3 poor weight gain; failure to make a quick return to normal after an infection, or failure to respond to appropriate antibiotic therapy;

4. abnormal chest radiograph suggestive of TB; and
5. laboratory findings suggestive of TB (histological, cytological, biochemical, immunologic, radiologic and/or molecular).

b. Probable Tuberculosis

A probable case of tuberculosis is one where signs and symptoms of tuberculosis are evident but the criteria for a diagnosis of clinical tuberculosis have not been met.

c. Confirmed Tuberculosis

A confirmed case of tuberculosis is one where a positive culture with or without a positive smear for M. tuberculosis is documented.

Study Population

Pediatric patients <19 years of age, with signs and symptoms suggestive of tuberculosis, with or without TB exposure, who were seen at the Philippine General Hospital Emergency Room, OPD Clinic, TB Clinic of the Section of Infectious and Tropical Diseases in Pediatrics, or admitted at the Pediatric Wards from July 2006 – September 2006, who were never given previous tuberculin skin tests, and who were willing to be tested were included in the study.

Those who were excluded were the following: Any person known to have a condition that could suppress delayed-type hypersensitivity such as human immunodeficiency virus infection, cytotoxic chemotherapy, systemic corticosteroid therapy; had live viral vaccination within the last 6 weeks; and were infected with measles, mumps, varicella, typhoid fever, whooping cough, and influenza within the last two months.[16]

Critically-ill and hemodynamically-unstable patients, as well as, those with no consent for Mantoux testing were excluded from the study.

Data Collection

Written informed consent was obtained from all subjects, who agreed to participate in the study.

Study participants, who were eligible, were asked at the time of tuberculin skin test placement on the following: age, sex, prior BCG

vaccination, history of risk factors for TB (exposure to persons with a high likelihood of TB transmission), and history of illness compatible with TB. The above data were recorded on a patient record form. Randomization proceeded; and it was done by the co-investigator by drawing of lots. Study participants were assigned to receive either 2 TU PDD RT-23 on the right forearm (5TU PPD-S on the left) or 2 TU PPD RT-23 on the left (5 TU PPD-S on the right). The reagents were subsequently prepared and handed over by the co-investigator to the principal investigator who was blinded on the reagents used and on the sites of injection.

Using a gauge 25 needle tuberculin syringe on a thoroughly-cleansed and dried injection site,, each study subject was given two simultaneous intradermal injections of 0.1 ml 2 TU PPD RT-23 and 0.1 ml 5 TU of a commercial PPD preparation on the upper third of the volar surface of each forearm. A pale wheal, 6-10mm in diameter, was evident after injection. All intradermal injections were performed by the principal investigator.

The reagents were stored in a refrigerator located at the TB clinic of the Section of Infectious and Tropical Diseases in Pediatrics. They were kept cold (2-8 ° Celsius) and were protected from light at all times. Aseptic technique was observed when aspirating test doses.

Seventy two hours from the time of tuberculin administration, the transverse diameter of induration across the long axis of the forearm was measured through the palpation method by using a standard ruler and was recorded in millimeters by the principal investigator. The readings on the left and right forearm were initially recorded at the back of the patient record form. Transfer of data was done at the end of the study, so that at the time of reading, the investigator was still unaware of the PPD reagent used on either arm. The presence of additional features such as blisters, bullae, or lymphangitis were noted as observations on the patient record form.

Using 2 TU PPD-RT 23 or 5 TU PPD read at 72 hours, and regardless of BCG status, an induration of ≥ 5mm was considered positive when any of the following were present: history of close contact with a known or suspected infectious case of TB; clinical findings suggestive of tuberculosis; chest x-ray findings suggestive of tuberculosis; and immunocompromised condition. Otherwise, an induration of ≥ 10mm was considered positive.
Other ancillary procedures done on the study subjects, such as chest x-ray and the laboratory findings suggestive of TB (histological, cytological, biochemical, immunologic, radiologic, and/or molecular) were documented.

Outcomes Measured

The following were evaluated from the study:

1. Correlation between the skin test reactivity to 2 TU PPD RT-23 and to 5 TU PPD-S;
2. Mean reaction sizes and distribution of reaction sizes of the two tuberculin reagents in the study subjects;
3. Correlation between tuberculin reactivity and age, gender, nutritional status, presence of BCG vaccination, exposure, and clinical manifestations.

Statistical Analysis with Sample Size Estimate

The sample size was calculated with the following considerations:

R0 = 80.0
R1 = 92.8
α = 1%
β = 5%
n=63 for correlation analysis

Data were summarized using frequency tables and percentages. Intraclass correlation was done between the readings obtained for 2 TU PPD RT-2 3 and 5 TU PPD. The effect of age on tuberculin reactivity was analyzed using the t-test. Correlation between tuberculin reactivity and sex, nutritional status, and clinical manifestations were determined by chi-square analysis. Correlation between tuberculin reactivity, BCG, and TB exposure

were determined by Fisher's Exact Test. A p value of < 0.05 was considered statistically significant.

Ethical Considerations

The study was registered at the Research Implementation and Development Office of the College of Medicine, University of the Philippines Manila. Eligible patients were voluntarily recruited and a written informed consent was obtained from the parent or guardian of the study participants prior to tuberculin skin testing.

RESULTS

From July 18 to September 1, 2006, 97 patients were seen at the TB Clinic for tuberculin skin testing. Of these, 74 patients (76.3%) were eligible and were included in the study. Sixty five of the seventy four (87.8%) reported after 72 hours for Mantoux test reading. They were included in the final data analysis.

There were 40 male and 25 female patients with a M: F ratio of 1.6:1. The mean age is 6.4 ± 4.4 years (mean ± SD), range of 8 months to 18 years.

Majority of the study participants had normal weight for height (64.6%), and the rest had some degree of protein-energy malnutrition. Most had mild stunting (33.8%) or had normal height-for-age (27.7%).

The study participants were mostly from the out-patient clinics (n=54), and the rest were referrals from the pediatric wards and emergency room.

Majority of those tested were from Metro Manila comprising 67.7% of patients in the study. The rest came from nearby provinces such as Cavite, Laguna, and Bulacan (32.3%).

Fifty seven (87.7%) of the study participants had a history of BCG vaccination, six (9.2%) had no such history, and two (3.1%) had unknown BCG status.

As to exposure to an adult with tuberculosis, 42 (64.6%) of the study participants had no known exposure, while 23 (35.4%) had known exposure. Of those with known exposure, 16 (24.6%) were exposed to adults with confirmed tuberculosis. Ten of these adult contacts had positive sputum and chest x-ray studies, two had positive sputum studies but had unknown chest x-ray results, three had positive chest x-rays but unknown sputum studies, and one had a positive chest x-ray and a negative sputum study. Seven (10.8%) claimed to have been exposed to adults with tuberculosis.

Table 1. Demographics of Patients Enrolled

	N	%
Sex		
Male	40	61.5
Female	25	38.5
Age in Years		
0-5 years	33	50.8
6-10 years	22	33.8
11-15 years	7	10.8
≥ 16 years	3	4.6
Nutritional Status		
Wasting		
Normal	42	64.6
Mild	14	21.5
Moderate	5	7.7
Severe	0	0
No data *	4	6.2
Stunting		
Normal	18	27.7
Mild	22	33.8
Moderate	13	20.0
Severe	9	13.8
No data *	3	4.6

* Refused height or weight determination.

Table 3. Distribution of Subjects as to Source of Referral

Source of Referral	N	%
Out-Patient Clinic	54	83.1
Pediatric Wards	9	13.8
Pediatric Emergency Room	2	3.1

Table 4. Distribution of Subjects as to Presence of BCG Vaccination

Presence of BCG Vaccination	N	%
Yes	57	87.7
No	6	9.2
Unknown	2	3.1

Table 5. Distribution of Subjects as to TB Exposure

Exposure	N	%
No	42	64.6
Yes (confirmed)	16	24.6
Yes (claimed)	7	10.8

Table 6. Mean PPD size for 2 TU PPD RT-23 and 5 TU PPD-S in those with (claimed and confirmed) and without TB exposure

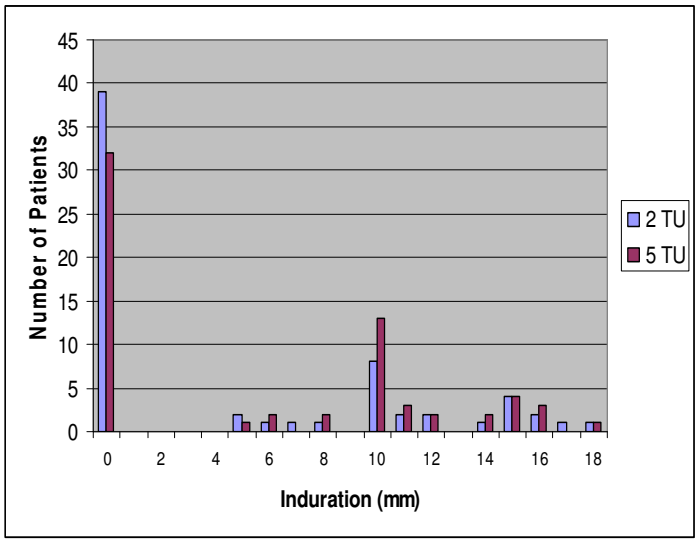
	Mean PPD Size		
2 TU with exposure (claimed)	6.5 mm	8 mm	5 TU with exposure (claimed)
2 TU with exposure (confirmed)	5.8 mm	6.4 mm	5 TU with exposure (confirmed)
2 TU without exposure	3.7 mm	5.1 mm	5 TU without exposure

Presence of lymphadenopathies, weight loss or failure to gain weight, prolonged cough and fever were the most common clinical features noted.

Of the 65 study participants, 32 (49.2%) had readings for both the 2 and 5 TU doses recorded as zero, while 15 (23.1%) had equal readings for both the 2 and 5 TU doses other than zero. The 5 TU dose gave a larger reading than the 2 TU dose in 14 cases (21.5%), but in 4 cases (6.2 %), the 2 TU reading was greater.

The distribution of tuberculin reactions is shown in Figure 1.

Figure 1. Distribution of tuberculin skin test reactions in 65 pediatric patients with clinical manifestations of tuberculosis tested with 2 TU PPD RT-23 and 5 TU PPD



Mean induration for 2 TU PPD was 4.7mm ± 6.1 mm, while that for 5 TU PPD was 5.8 mm ± 6.1 mm.

The minimum recorded reading for both the 2 TU and 5 TU PPD was 0 mm and the maximum was 18 mm.

Mean difference in paired reaction size between 2 TU and 5 TU tuberculin was -1.02 mm ± 2.8 mm (range of -11 to 3 mm).

Table 7. Difference between Paired Tuberculin Responses

Difference	Frequency	%
-11	1	1.5
-10	3	4.6
-6	1	1.5
-5	3	4.6
-4	1	1.5
-3	1	1.5
-2	1	1.5
-1	3	4.6
0	47	72.3
1	2	3.1
3	2	3.1

Using the present guidelines in the country today to determine a positive tuberculin skin test 27 (41.5 %) patients would have been

considered positive with 2 TU and 33 (50.8 %) with 5 TU. Six reactions (9.2%) were not detected by 2 TU which were detected by 5 TU.

Table 8. Tuberculin Reactivity of Study Participants to 2 TU and 5 TU tuberculin

	2 TU positive	2 TU negative	Total
5 TU positive	27 (41.5%)	6 (9.2%)	33 (50.8)
5 TU negative	0	32 (49.2%)	32 (49.2%)
Total	27 (41.5%)	38 (58.5%)	65 (100%)

PPD skin test reactivity with the two reagents was highly correlated (intraclass correlation 0.88; 95% CI 0.83-0.94).

There was no significant association between age, gender, nutritional status, presence of BCG vaccination, and TB exposure with reactivity to 2 TU tuberculin.

There was likewise no association noted between any of the clinical manifestations and reactivity to 2 TU tuberculin.

Of the 65 patients tested, 18 (27.7%) had positive tuberculin skin tests which turned out to be confirmed cases of tuberculosis, while 8 (12.3%) were probable TB cases. Of those whose tuberculin skin tests were read as negative, eight (12.3%) were diagnosed upon completion of work-up not to be cases of tuberculosis. Seven (10.8%) turned out to be confirmed cases of TB, and sixteen (24.6%) were probable cases of TB.

Six cases were detected by 5 TU PPD but were missed out by 2 TU PPD. Four of these (6.2%) PPD turned out to be confirmed cases of tuberculosis while 2 (3.1%) were probable cases. The outcomes of two patients were not determined due to incomplete work-up.

Table 9. Association between Demographic Features with Reactivity to 2 TU Tuberculin

Variable	PPD Positive		PPD Negative		p-value
	N	%	N	%	
Age	27	41.5	38	58.5	
Sex					0.176 (NS)
Male	14	35.0	26	65.0	
Female	13	52.0	12	48.0	
Nutritional Status					
Wasting					0.388 (NS)
Normal	15	35.7	27	64.3	
With Wasting	9	47.3	10	52.6	
Stunting					0.883 (NS)
Normal	7	38.9	11	61.1	
With Stunting	18	40.9	26	59.1	
Presence of BCG Vaccination					0.678 (NS)
With BCG	24	42.1	33	57.9	
Without BCG	2	33.3	4	66.7	
TB Exposure					0.415 (NS)
With Exposure (claimed)	4	57.1	3	42.9	
With Exposure (confirmed)	8	50.0	8	50.0	
Without Exposure	15	35.7	27	64.3	

Table 10. Association between Clinical Features with Reactivity to 2 TU Tuberculin

Variable	PPD Positive		PPD Negative		p-value
	N	%	N	%	
Cough					0.285 (NS)
With Cough	15	48.4	16	51.6	
Without Cough	12	35.3	22	64.7	
Fever					0.851 (NS)
With Fever	12	42.9	16	57.1	
Without Fever	15	40.5	22	59.5	
Adenopathy					0.941 (NS)
With Adenopathy	18	41.9	25	58.1	
Without Adenopathy	9	40.9	13	59.1	
Night Sweats					0.447 (NS)
With night sweats	11	47.8	12	52.2	
Without night Sweats	16	38.1	26	61.9	
Weight Loss					0.179 (NS)
With weight loss	20	47.6	22	52.4	
Without weight Loss	7	30.4	16	69.6	
Anorexia					0.771 (NS)
With Anorexia	9	39.1	14	60.9	
Without Anorexia	18	42.9	24	57.1	
Failed Recovery					0.135 (NS)
With	0	0	3	100.0	
Without	27	43.5	35	56.5	
Failed Response to Antibiotics					0.723 (NS)
With	2	50	2	50	
Without	25	41.0	36	59.0	
Extrapulmonary Symptoms					0.867 (NS)
With	8	40	12	60	
Without	19	42.2	26	57.8	

(NS) – Not Significant

Table 11. Tuberculin Reactivity with 2 TU PPD RT-23 and 5 TU PPD-S and TB Disease

	Confirmed TB		Probable TB		Not TB	
	N	%	N	%	N	%
Positive TST for both 2 TU and 5 TU	18	27.7	8	12.3	0	0
Positive TST with 5 TU alone	4	6.2	2	3.1	0	0
Negative TST for both 2 TU and 5 TU	7	10.8	16	24.6	8	12.3

DISCUSSION

Tuberculosis to this day remains to be a continuing medical and social problem ranking sixth as a leading cause of morbidity and mortality in the Philippines.[17] It remains to be "the great mimic" due to its protean manifestations.

Several diagnostic tests have been developed to aid in the detection of TB infection and disease. Nucleic acid amplification techniques (e.g. PCR), serodiagnostic methods (e.g. Elisa kits), and T-cell based assays (e.g. interferon-gamma assay) have been introduced but are not recommended for routine diagnosis of pulmonary tuberculosis in children due to its various limitations. These include its high cost, limited local availability (for PCR), low sensitivity (for ELISA), with only a few studies involving children. Thus, the tuberculin skin test cannot be replaced just yet by these assays.[18]

In contrast, Mantoux testing remains to be a readily available procedure in the detection of TB infection, and is widely used in epidemiologic surveys, evaluation of contacts of patient with active tuberculosis, selection of persons for chemoprophylaxis, and surveillance of healthcare workers for TB infection. Unfortunately, the tuberculin skin test is dependent on many variables which may affect its interpretation and result. [19]

There have been reported discrepancies between results obtained with the use of different tuberculins.

A paired comparison of tuberculin skin test results in healthcare workers using 5 and 10 TU tuberculin showed a slightly larger reading with 10 TU than 5 TU, with a mean difference of 1.5 mm between the two doses.

Utilizing the 2 TU and 5 TU tuberculin, simultaneous comparison of reactivity to PPD RT-23 and Tubersol (a commercial PPD preparation bioequivalent to 5 TU PPD-S) in workers in Brazil showed the two reagents to be highly correlated (rho=0.92, P=0.01). [7] These findings have been previously demonstrated in Mexico in 1998 which showed that 2 TU of RT-23 gave very similar results to 5 TU Tubersol.[20]

Locally, a study done to evaluate 2 TU vs 5 TU PPD for determining tuberculin reactivity among children in a day care center showed a significant difference between the two doses. Twenty six percent (26%) of reactions were not detected by 2 TU while only four percent (4%) were missed by 5 TU (N=134). This study utilized two investigators administering either of the two reagents on one arm, and subsequently reading either of the reactions after a 72 hour period.[21]

In another local study comparing tuberculin reactivity of children with pulmonary tuberculosis to 2 TU PPD RT-23 vs 5 TU PPD-S, 43.7% of those given 5 TU were read as positive compared to only 10.7% of those given 2 TU (N=60).[22] This study utilized only one investigator giving all the tuberculin tests in both groups of patients randomized to receive either 2 TU or 5 TU tuberculin while a second investigator read the results after 72 hours.

To standardize experience and technique in application and reading of the test, a single investigator administered the test reagents in this study, unaware of the tuberculin dose and formulation being used. An intraclass correlation of 0.88 was obtained (95% CI 0.83-0.94) showing the two tuberculins to be highly correlated.

Taking into account the variables which may affect tuberculin reactivity, this study showed that age, gender, nutritional status, presence of BCG vaccination, TB exposure, and clinical manifestations were not factors influencing the size of the PPD reaction.

Age is not a factor influencing tuberculin reactivity. This is in contrast to the findings seen previously in local studies by Bonus and Gonzales which showed that the older the patient, the greater the chance of having a significant PPD reaction signifying increased TB exposure with age.

Gender is not a factor influencing tuberculin reactivity. This is consistent with previous findings particularly in children that the

incidence of tuberculosis is not significantly different in girls and boys

Nutritional status is not a factor influencing tuberculin reactivity. These were the same findings noted in a local study by Gonzales et. al. However, in the study of Bonus in 1991, a significant difference in PPD reactivity was found between first degree vs second degree malnutrition. This reinforces the previous understanding that malnutrition contributes to the occurrence of false negative tuberculin skin test reactions.

Presence of BCG vaccination is not a factor influencing tuberculin reactivity. It was earlier believed that previous BCG vaccination can account for PPD positivity depending on the interval between BCG and tuberculin skin test administration. Community based studies however have shown that tuberculin reactivity were similar among those vaccinated in infancy and those who were never vaccinated. The same findings were noted in the study of Gonzales where no association was noted between BCG and tuberculin reactivity.

Exposure to an adult whether claimed or confirmed is not a factor influencing tuberculin reactivity. This is in contrast to the findings obtained by Tanchuan and colleagues which revealed that 52.1% of children in contact with sputum positive cases and 43.1% of those exposed to chest x-ray positive cases were positive PPD reactors.[23]

Not one of the clinical manifestations of the study participants was found to be a factor influencing tuberculin reactivity although previous studies have shown that persistent cough, history of contact with a case of TB, low weight for age, and prolonged fever (in addition to a positive tuberculin skin test) were the most relevant predictors of disease in children.[24]

The tuberculin skin test although not 100% sensitive and specific (missing 10.8% confirmed cases, and 24.6% probable cases of TB in this study), still remains to this day the most practical means of detecting TB infection. A negative test never rules out TB infection or disease. It should always be interpreted in the context of an accurate history of exposure to an adolescent or adult case of TB, a thorough search for the presence of clinical manifestations suggestive of TB, employment of diagnostic aids particularly chest radiography, and most importantly use of sound clinical judgment.

CONCLUSIONS

Tuberculin skin test reactivity among children with clinical manifestations of tuberculosis tested with 2 TU PPD RT-23 and 5 TU tuberculin were found to be comparable, with an intraclass correlation of 0.88 (95% CI 0.83-0.94); thus 2 TU PPD can be used to replace 5 TU PPD in routine Mantoux testing.

Taking into account the variables which may affect tuberculin reactivity, this study showed that age, gender, nutritional status, presence of BCG vaccination, TB exposure, and clinical manifestations were not factors influencing the size of the PPD reaction.

RECOMMENDATIONS

A large-population, multi-center, randomized, placebo-controlled trial should be conducted to obtain statistically significant evidence.

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