The Booster Phenomenon of Tuberculin Skin Testing in Patients Receiving Hemodialysis

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ABSTRACT

Background: The risk of developing tuberculosis is high among chronic hemodialysis patients. The tuberculin skin test (TST) has been in use for diagnosing latent TB, but few data are available on TST in hemodialysis patients. **Objective:** This study was done to identify the TST reactivity and frequency of booster effect in serial TST among hemodialysis patients. **Methods:** A total of 100 patients in three hemodialysis centers were prospectively tested. Patients with less than 10mm indurations were given additional TST one and four weeks later to determine the frequency of booster effect. **Results:** The cumulative prevalence of a positive TST was 7 % for the first test and 16 % for the third test. There was a weak, but significant correlation between TST positivity, serum albumin level, urea reduction ratio and KT/V ($p<0.05$). There was no influence of age, gender, hemodialysis duration and primary renal disease. **Conclusion:** This study showed that the TST reactivity and booster effect among our hemodialysis patients in Iran are lower than in other societies. Inadequate hemodialysis and poor nutrition may contribute to the lower tuberculin skin test reactivity in our hemodialysis patients.

Keywords: Hemodialyses, Mycobacterium Tuberculosis, Tuberculin Test

INTRODUCTION

An increased awareness of the need for good screening methods for mycobacterium tuberculosis infection is necessary due to increased prevalence of tuberculosis (TB) during the last two decades in the world (1).

Hemodialysis patients are at risk to develop TB disease 6 to 16 times more frequently than other members of the community due to impaired cellular immunity in chronic renal failure and an increase in the likelihood of progression from latent infection to active disease (1, 2).

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Therefore, it is important to evaluate the tuberculin skin test (TST) in the hemodialysis population and to compare it with other screening methods to optimize the detection of infected persons and to treat the latent TB infection (3).
Few data are available on TST reactivity in hemodialysis patients (1,4,5). Routine TST has not been performed in hemodialysis patients because of high rates of anergy in patients with chronic renal failure. Uraemia alters the macrophage function, which can lead to anergy for skin tests (6).
The primary aim of this prospective study was to evaluate the frequency and significance of the booster phenomenon in serial tuberculin testing in hemodialysis patients.

SUBJECTS AND METHODS

A total of one hundred patients have been recruited from three University hemodialysis units of Fars province in Iran. The patients who entered the study were all more than 18 years old and underwent hemodialysis for an average of 3-4 hours, 2-3 times a week for more than 3 months.
Patients with acute, intercurrent illness or hospitalization in the last month, recent use of corticosteroid or immunosuppressive drugs in the last two weeks, current plasmapheresis, immunoglobulin or blood product transfusion in the last week, immigration from other countries and previous tuberculosis infection were excluded.
The patients were given an elaborated discussion on tuberculosis skin test (TST) before starting the test, and were asked to give written consent for the tests.
Patient charts were reviewed for demographic information (age, sex, duration of hemodialysis, cause of renal failure), medical history (including drug history, history of blood product transfusion in the last month, history of acute illness or hospitalization in the last month and the history of previous TB), and for laboratory tests (Urea reduction ratio, KT/V ratios and calcium, phosphorous and albumin concentrations). No specific program of TST had been implemented previously in our HD canters.
The TST with the mantoux method was performed interadermally on the volar surface of the forearm that did not have the arteriovenous shunt using 0.1 ml (5 TU) of PPD material (0.1ml of Razi PPD solution, Lotno-16-6-8).
All skin tests were done at least 30 mm away from any lesions and scars or visible veins.
Implantation by intradermal injection using a standard 26 gauge 1-ml bevelled needle and plastic syringe was considered correctly done only if a 6-10 mm wheal was observed at the injection site. Responses were read 48-72 hours later by an experienced reader using the ball point method to measure the areas of induration by drawing a line around the area of induration and noting an increase of resistance to movement by the pen when the borders of the indurate region were reached**.**
Indurations of 10 mm or more were considered significant. To determine the booster phenomenon, all patients with less than 10 mm induration in the first TST were given a second TST, 7 days later. The booster phenomenon was defined as positive if induration from the second TST was 10 mm or more or had at least a 6 mm increase in the measured induration compared to the first TST (7).
Additional TST (third time) was done 4 weeks after the first one for the patients having less than 10 mm induration in the second time and the responses were observed to see if any additional boosting effects were present by time.

Patients with a positive TB skin test underwent all investigations for active tuberculosis including chest x-ray and were recommended to take isoniazide if investigations were negative. Statistical analysis was done by SPSS version 14 and P-Values less than 0.05 were considered significant.
Analysis of risk factors for positive TST was performed using Mann-Whitney nonparametric analysis and Spearman's Rho correlation test.

RESULTS

A total of one hundred patients (52 women and 48 men) were included in this study. The underlying diseases and demographic characteristics are illustrated in Table 1. Only 7% of the patients showed a positive reaction after the first TST and the second TST did not add any more positive reactions. Booster effect of the third test resulted in a 9% increase in positive TST reactions with a total of 16% positivity.

Table 1. Patients' demographic characteristics and underlying diseases

Characteristics	Mean	Range
Sex	48% male	
Age (years)	54 ± 14.85	18-78
Duration of hemodialysis (months)	36.5 ± 34.8	3- 217
URR	63.3 ± 14 %	13-90
Weekly KT/V	2.87±0.89	1.3 – 5.6
Albumin G/l	4.3± 0.5	3-5
Calcium	8.8 ± 1.1	6-11.5
Phosphorous	5.2± 1.7	3-10.8
Underlying disease	**No.**	**Percentage**
Hypertension	29	29 %
Diabetes mellitus	25	25 %
Glomerular disease	16	16 %
Unknown etiology	14	14%
Nephrolithiasis	14	14%
Reflux nephropathy	2	2 %

The mean size of induration was increased significantly in TST-3 compared with that of TST-1 (3.04 mm versus 3.11 mm, $p<0.001$)(Table2).

Table 2. Comparison of indurations in three consecutive tuberculin skin tests (TST)*

Size of induration	Test number		
	Initial TST TST-1	One week TST TST-2	4 week TST TST-3
0	17	15	6
1-5	74	74	73
6-9	2	4	5
≥10	7	0	9
Mean induration (millimeter)	3.04±3.3	2.47±1.7	3.11±2.6[a]

*Ninety three patients with indurations less than 10 mm after the initial TST had a second and a third tuberculin test after 7 days and 4 weeks, respectively.
[a]The mean size of induration was increased significantly in TST-3 compared with that of TST-1 (3.04 mm vs 3.11 mm, $p< 0.001$).

For TST-1, URR was only correlated with TST positivity (p=0.039; R=0.20). Positive TST results (cumulative results of all three tests) were significantly but weakly correlated with the serum albumin level, weekly KT/V and URR (Table 3).
Comparing the patients with a negative TST (when combining the results of the three tests) to patients with a positive TST, we found a significant relationship between serum albumin, urea reduction ratio and KT/V with TST positive reactivity (p<0.05).

Table 3. Correlation analysis between positive TST results (Cumulative result of the three tests) and risk factors

	Spearman's rho	P-Value
Age	0.084	0.40
Sex	0 .037	0.71
Renal disease	0.031	0.75
Time on dialysis	0.102	0.31
Clacium	0.102	0.31
Phosphorous	0.134	0.18
KT/V	0.199	0.047
Alb	0.232	0.028
URR	0.235	0.019

DISCUSSION

Hemodialysis patients are at increased risk of tuberculosis (8, 9). Periodic TST may be useful for surveillance of these high risks patients (10). The tuberculin skin test is not so predictive of developing tuberculosis disease because of its limitations such as cross reaction with other mycobacterial antigens, application or reading errors and abnormal immune response of the patients (11, 12).
Despite these difficulties, the TST is an applicable method for detecting latent TB infection. Tuberculin skin positivity in Iranian population varies between 15- 34% (13-15).
Tuberculin skin test positivity of our hemodialysis patients was about 7% and cumulative positive results after the booster effect was 16%.
Wauters et al., in a study on hemodialysis patients in Belgium, have shown a 15% rate of TST positivity in the first test which is comparable with other studies performed on hemodialysis patients in North America (1,4,5). The cumulative rate after four repeated tests increased to 32.6% (1).
Akcay et al., in their study in Turkey, have shown a 35.8% rate of TST positivity after the initial TST. The boosting effect was detected in 29.4% of the patients (2).
In a study on hemodialysis patients in Iran, Khosroshahi et al. have shown a positive tuberculin skin test in 19.9 % of kidney recipients with a single TST (16).
Despite having older patients (mean age of patients, 54 ± 14.8), our cumulative TST results (16 %) are comparable with those of Khosroshahi et al. (mean age of the patients, 40 ± 14.7).
It is worth mentioning that the patients of Khosroshahi et al. were kidney recipients who were in a better general health.
When evaluating risk factors that can influence TST results, no significant correlation between age, sex, cause of renal failure, hemodialysis duration, serum calcium and phosphorus levels with the TST reactivity was found, but there was a significant correlation between serum albumin, urea reduction ratio and weekly KT/V with TST positive reactivity.

Therefore, it appears that we have established a correlation between TST positive reactivity with dialysis efficiency and the nutritional status of patients considering serum albumin level to be a nutritional marker in hemodialysis patients.
In conclusion, in our study, significant rates of TST positivity and booster effects among hemodialysis patients are shown. Inadequate hemodialysis and poor nutrition may contribute to the lower tuberculin skin test reactivity in our hemodialysis patients.
Even with a high rate of anergy, TST seems to be useful among HD patients; it is also inexpensive and easily performed.

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