Original Article

Identifying predictors of treatment outcome in Tuberculosis

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Abstract

Background: Response to the treatment can be gauzed from the symptomatology, anthropometry, clinical parameters, and simple laboratory investigations in patients on anti-tuberculosis treatment as per Revised National Tuberculosis Control Programme (RNTCP) guidelines. Those who are not showing improvement in the parameters can then be selectively subjected to Cartridge Based Nucleic Acid Amplification Test and further intensive monitoring & follow-up. **Materials and Methods:** The project was undertaken in the one District of Maharashtra State from July 2017- to December 2018. The experts specifically identified parameters to be monitored in the field and specially trained Senior Treatment Supervisors workers (STS) followed up 100 newly diagnosed patients with Tuberculosis fortnightly during the Intensive Phase and monthly thereafter till completion of the 6-month treatment. **Results:** There was no significant difference in the patients according to age, sex, religion, education, occupation, and socio-economic status. The increase in weight, body mass index, chest circumference during inspiration and expiration, mid-arm circumference, and hemoglobin from the commencement of treatment to completion showed a significant positive correlation. A negative correlation was found with body temperature, pulse rate, respiratory rate, lymphocytic count, and Erythrocyte Sedimentation Rate. There was no correlation with the blood sugar level. **Conclusion:** This study has observed that objective parameters of gain in weight, reduction of fever, improvement in chest expansion, reduction in pulse and respiratory rate, respiratory rate are significantly associated with favorable outcome after a standard daily regimen under RNTCP. STS workers can easily monitor these parameters during their home visit.

Keywords: Revised National Tuberculosis Control Programme, Cartridge Based Nucleic Acid Amplification Test, Senior Treatment Supervisors, Intensive Phase, Erythrocyte Sedimentation Rate

Introduction

India has a very high prevalence of Tuberculosis (TB). According to the global TB report 2015, the prevalence of TB is 2.5 million (195 lakh/year)[(1)]. It is also true that India has a very high mortality due to TB and very high Multi-Drug Resistant (MDR) TB. The Revised National Tuberculosis Control Programme (RNTCP) was launched in 1997 with an objective of achieving an 85% cure rate[(2)]. World Health Organization (WHO) released a stop TB strategy in 2006[(3)]. India adopted the components of the "Stop TB strategy". In 2007 joint TB and Human immunodeficiency virus (HIV) collaborative activities were started, which were redefined in 2008 that emphasized programmatic management of drug-resistant (DR) TB[(4)].

Nucleic Acid Amplification Test (NAAT) provides an accurate and rapid diagnosis of TB by detecting *Mycobacterium tuberculosis* (*M. tuberculosis*) and Rifampicin (Rif) resistance-conferring mutations in sputum specimens as well as a specimen from extra–pulmonary sites. Presently, under RNTCP, its use is recommended for diagnosis of DR – TB in presumptive DR – TB patients and TB preferentially in key populations such as children, People living with HIV (PLHIV), and extrapulmonary TB[(5)].

Under the national TB programme State of Maharashtra has been identified for a daily regimen of TB instead of Directly Observed Therapy Short Term (DOTS) in the year 2016 – 2017[(6)]. It is observed that about 80% of the sputum positive cases of TB become sputum negative by the end of the Intensive phase (IP), and about 20% of cases take longer to become sputum negative. All of these are not cases of MDR – TB. Cartridge Based Nucleic Acid Amplification Test (CB NAAT) is used to identify MDR- TB for rapid molecular diagnosis. Some simple parameters based on symptomatology, anthropometry, and biochemical and

pathological tests can be undertaken periodically to find out the response to TB treatment. Improvement seen in the parameters during IP indicates that the patient responds to the treatment. Simple clinical parameters like continued pyrexia and inability to gain weight can identify a person not responding to treatment well in advance of completion of IP so that selectively such persons can be subjected to further clinical evaluation and management. This early identification of MDR TB will enable us to commence the second line of treatment early, which will benefit the patient and prevent the spread of MDR TB.

Objective

The objective of this study was to find out essential parameters and knowledge that STS workers can monitor to indicate the adverse outcome of newly diagnosed cases of TB.

Material and Methods

A prospective follow-up study of all newly diagnosed TB cases from all Tuberculosis Units (TUs) of one District, Maharashtra, were included in the study. Institutional ethics committee of Krishna institute of medical sciences (deemed university), Karad has given ethical sanction for this project. Data was collected in July 2017 and was completed in December 2018. Consent was obtained from all the patients participating in this study. The working definitions used as well as the treatment given to all TB cases including MDR TB in this project, were as per RNTCP guidelines[7].

Exclusion criteria

All MDR, Extensively drug-resistant (XDR), patients not giving consent for participation in the study, and very sick and moribund patients were excluded from the study.

Sample size estimation and sampling

A prospective follow-up study of all newly diagnosed TB cases from all tuberculosis units of one District, Maharashtra, were included in the study.

Data collection

Training of all 11 STS and 7 Senior TB Laboratory Supervisors (STLS) workers was done for two days to enable them to fill up the proforma prepared for data collection. Information about education, occupation, income, caste, marital status, diabetes, hypertension, alcohol drinking, and use of tobacco in smoking and nonsmoking forms was collected from all newly diagnosed cases included in the study. The patients were classified as Above Poverty Line (APL) and Below Poverty Line (BPL) by their possession of color-coded ration cards. Yellow cards are indicated below the poverty line, and orange and white cards are indicated above the poverty line. Any other significant illnesses, including HIV and diabetes, were identified, and appropriate management was undertaken. The standard procedures of taking all the anthropometric measurements and recording the axillary body temperature by standard mercury thermometer were demonstrated. The correctness of the methodology used by individual STS workers was tested and ensured. The follow-up was done by the STS workers during their home visits, and x-ray and laboratory investigations were done when the patients visited the respective TUs.

Follow-up

All patients enrolled were examined and followed up fortnightly for eight weeks of intensive phase and monthly thereafter till their completion of treatment of six months. Laboratory tests were repeated every two months. Information related to the following parameters was collected. In this study, all patients were followed up for the study period.

1. Symptomatic parameters: Included appetite (poor/ good/ improved/ not improved) and breathlessness (present/ absent)
2. Anthropometric parameters: Included height in cm (measured using a measuring tape), weight in kg (measured using the standard weighing machine), Body Mass Index (BMI) as per WHO criteria, chest circumference, daily inspiration and expiration in cm, mid-arm circumference in cm
3. Clinical parameters: Included body temperature in ^{0}C, pulse rate, respiratory rate, lymphadenopathy
4. Laboratory parameters: Included hemoglobin in gm%, Lymphocyte count, Erythrocyte Sedimentation rate (ESR) by Westergren method, Blood sugar (mg/dl)

Sputum examination and x-ray chest were repeated at the end of the intensive phase of treatment as per RNTCP guidelines.

Results

There were 100 cases of TB included in the study, of which 70% were sputum positive pulmonary TB cases, 19% were x-ray positive cases, and 11% were extrapulmonary cases. There were three deaths and 2 cases of MDR, so the conversion rate was 92.8% (NB Conversion rate only applies to sputum positive cases). In the extrapulmonary and x-ray positive cases, all completed treatment. Table 1 shows the age and sex distribution of the study population as below.

Table 1: The age and sex distribution of the study population

Age groups (years)	Males		Females		Total	
	N	%	N	%	N	%
<12	1	2.04	1	1.96	2	2
12-20	6	12.24	11	21.57	17	17
21-30	14	28.57	16	31.37	30	30
31-40	11	22.45	6	11.76	17	17
41-50	5	10.20	10	19.61	15	15
51-60	6	12.24	2	3.92	8	8
>60	6	12.24	5	9.80	11	11
Total	49	100.00	51	100.00	100	100

There were two pediatric patients below the age of 12 years. They were X-ray positive, and both have completed the treatment as per RNTCP guidelines. The most typical age group was 16-30 years, and the least common was <15 years. It was found that females were apparently more than males among TB cases. However, the age and sex distribution were not statistically significant (χ^2 =6.79, p= 0.34). Most TB patients, i.e., 36%, had completed secondary schooling. Only 2 (2 %) were uneducated. There was no significant difference in the distribution of TB cases according to educational status. (χ^2 =7.05, p= 0.96). The majority of the female patients [22, (71%)] were homemakers, followed by agriculture and farm laborers. There was no significant difference according to the occupation of the patient. (χ^2 =26.43, p= 0.09). The commonest religion was Hindu (87%), followed by Buddhist (10%). Only 3 cases (3%) were Muslims. Caste distribution revealed that the maximum number of patients were Marathas, followed by SCs. There were 36% of patients below poverty line. There was no significant difference according to the socio-economic status of the patient. (χ^2=7.65, p=0.27).

There was only one patient who was both a smoker and consumed alcohol. The use of non-smoke tobacco was very high, i.e., 31%, and smokers were 4%. There was no known coexisting disease in 75 cases, anemia in 6, HIV in 4, and hypertension in 1 case. As judged by patients' knowledge, awareness indicated that 56% knew they were suffering from TB, and the rest, 44%, did not know it.

Since there were only five patients with TB who had adverse outcomes, three deaths, and two MDR, it could not be tested statistically with the characteristics of the patients due to minimal numbers. However, in the cured patients, all parameters showed statistically significant improvement before and after treatment. The mean values with standard deviation and the direction of change are shown in Table 2. Mean gain in weight was 4.32 kg with SD of 0.24 kg, while mean BMI also showed a significant improvement of 1.26 kg/m^2 with SD of 0.51 kg/m^2. The reduction in body temperature by 1.59^{0}C with SD of 1.75^{0}C was significant, although there was much variation in the observations. Improved chest circumference in patients with pulmonary TB was significant for both inspiration and expiration, the mean improvement being around 2 cm. Significant improvement in the mean mid-arm circumference of 1.78 cm was seen, although a higher SD of 1.79 cm indicated much variation. There was a significant mean reduction in pulse rate, respiratory rate, lymphocyte count and ESR. The mean Hb gm % levels showed a significant improvement (1.47 gm %). The blood sugar level did not significantly differ before and after treatment.

Table 2: Comparison of Parameters among TB Patients at Diagnosis and at the End of the Treatment

Sr. No.	Parameter	Mean values at diagnosis	Mean values at completion of treatment	Mean difference	t	P
1	Weight (kg)	43.80±9.34	48.13±9.58	4.32±0.24	15.66	<0.0001
2	BMI (kg/m^2)	17.08±3.25	18.46±3.16	1.26±0.51	11.1	<0.0001
3	Body temperature (°C)	36.84±2.61	35.29±2.81	-1.59±1.75	7.11	<0.0001
4	Chest Circumference in Inspiration (cm)	72.48±20.38	73.41±21.54	2.03±1.63	9.35	<0.0001
5	Chest Circumference in Expiration (cm)	73.09±21.06	74.42±22.47	1.99±2.09	7.24	<0.0001
6	Mid arm circumference (cm)	20.63±3.71	22.63±3.71	1.78±1.79	7.56	<0.0001
7	Pulse rate (/min)	76.89±6.25	72.95±2.37	-3.94±5.11	6.16	<0.0001
8	Respiratory rate (/min)	24.78±3.76	21.55±3.23	-3.22±3.02	7.84	<0.0001
9	Hb (gm%)	9.31±1.35	10.75±1.14	1.47±1.07	11.16	<0.0001
10	Differential Lymphocyte count/ 100 Leukocytes	39.98±13.46	29.98±11.23	-10.00±6.15	11.26	<0.0001
11	ESR in mm by Westergren method	49.35±16.69	25.59±10.88	-24.39±12.29	14.58	<0.0001
12	Blood sugar (mg%)	100.07±26.78	100.58±13.28	-0.43±21.64	0.16	0.87

Discussion

In this study, we did not observe any association of favorable outcomes with age and sex of the patients, their educational status, occupation, religion, socio-economic status, use of tobacco, alcohol, or presence of HIV, diabetes, anemia, or blood pressure. None of the factors are shown to be associated with the outcome. This is a pilot study to determine which parameters STS workers can monitor during their home visits and when patient's visit to the TU have a significant correlation with the favorable outcome of the standard treatment under RNTCP for newly diagnosed cases of TB. We have found out that objective parameters of gain in weight, reduction of fever, improved chest circumference, reduction in pulse rate, respiratory rate, which can be monitored by the STS workers during their home visit as per their schedule specified under RNTCP are significantly associated with the favorable outcome after a standard daily regimen of TB under RNTCP. Monitoring of these parameters will need the provision of thermometers, weighing machines, and measuring tapes for each STS worker. Alternatively, STS workers can bring the patients to TU and take these readings in the TU. Simultaneously they can also be subjected to Hb estimation, Lymphocyte count, and ESR.

Studies from different parts of the world have observed a 3.4% to 19.4% case fatality ratio among newly diagnosed cases of Tuberculosis. Male to female ratio was found between 55:45 to 236:100 as compared to 49:51 in our study. Other workers observed successful treatment outcomes from 57.7 % to 57.5% compared to 92.8% in our study among sputum-positive cases[8-14].

In the present study, monitoring was done once a fortnight during IP and monthly thereafter. Suppose the patients are monitored at TU with these health parameters in addition to X-ray and sputum examination as per RNTCP guidelines; it will give a better indication of improvement in the patients' health. Any patient, not showing improvement at the end of IP and monthly thereafter can be subjected to CB NAAT to identify possible drug resistance.

As per the "National Strategic Plan for Tuberculosis Elimination 2017–2025," India is committed to eliminating TB by 2025. Identifying primary health care level markers like patient-reported symptoms, anthropometry, and clinical & biochemical indicators as predictors of treatment outcome will be very useful for this endeavor.

Limitations of the Study

The sample size was small, so an untoward outcome was observed in only five out of one hundred cases studied.

Conclusion

This study has observed that objective parameters of gain in weight, reduction of fever, improved chest circumference, reduction in pulse rate, respiratory rate, which can be monitored by the STS workers during their home visit, are significantly associated with the favorable outcome after a standard daily regimen of TB under RNTCP.

Recommendation

Regular follow-up of newly diagnosed patients put on an anti-tubercular regimen as per RNTCP guidelines should be done. STS workers should be provided with a measuring tape, weighing machines, and a clinical thermometer. This will help in the early identification of patients who are likely to have untoward outcomes. Deaths can be prevented by subjecting the patients to CB NAAT and providing expert care for possible complications. Early identification of MDR can benefit the patients by early commencement of second-line treatment and prevent the spread of drug-resistant strains of *tubercle bacilli*.

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