Original article ▌

ASSESSMENT OF LONG-TERM OUTCOME AMONG NEW SMEAR POSITIVE PULMONARY TB PATIENTS TREATED WITH INTERMITTENT REGIMEN UNDER RNTCP – A RETROSPECTIVE COHORT STUDY

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ABSTRACT

Background: Under the Revised National TB Control Programme (RNTCP) of India, treatment of TB is given as thrice weekly regimen following WHO recommended DOTS strategy and the success of treatment is largely declared based on completeness and bacteriological conversion. Once the patient is declared as cured or treatment completed, they are not followed up under the programme unless they come to the health system again with symptoms. Present study was conducted to assess status of patients at 2 years after successful anti-TB treatment under DOTS and to explore any potential impact of treatment irregularity on long term outcome

Methods: In this retrospective cohort study, all new smear positive (NSP) pulmonary TB cases declared as cured or treatment completed from were included in the study. They were interviewed, after 24 months from date of declaration of successful treatment, using semi-structured questionnaire. Patient TB treatment card and Tuberculosis registers were also used to collect desired information.

Results: A total of 657 out of 706 successfully treated NSP TB patients were included in the study. Out of these, 326 (49.6%) patients had any interruption during their treatment. The average number of doses missed during intensive phase and continuation phase was 7.5 and 11.9 respectively. Average duration of any interruption during treatment was 6.5 days. No significant difference was observed in proportion of treatment interrupters and non-interrupters across demographic variables except for a higher proportion of treatment interruption in patients enrolled from urban district. Out of 657 subjects, 71 (10.85%) had relapse of TB. Another 39 (5.9%) patients died due to TB. These unfavourable outcomes were not significantly different among treatment interrupters and treatment non-interrupters.

Conclusion: After being successfully treated, the new smear positive pulmonary TB patients had a very high proportion of relapse of TB. Treatment non-adherence was not significantly associated with long term unfavourable outcomes.

Keywords: Pulmonary Tuberculosis, RNTCP, Outcome, Treatment interruption

BACKGROUND

Any medical treatment course involving antibiotic, if taken irregularly or in sub-optimal doses, is a known risk factor for potential development of resistance to that antibiotic. This becomes more important when the treatment is longer and involves higher pill burden like anti-tuberculosis (TB) treatment. The therapeutic regimens given under the Directly Observed Treatment, Short course (DOTS) strategy as recommended by the World Health Organization (WHO) have been shown to be highly effective for both preventing and treating TB[1] but poor adherence to anti- TB medication is a major barrier to its global control [2,3,4]. Since treatment of TB under DOTS strategy in Revised National Tuberculosis Control Programme (RNTCP) follows thrice weekly regimen, adherence to regimen becomes more important as far as treatment success is concerned. In RNTCP, the success of treatment is largely declared based on completeness, and (smear microscopy based) bacteriological conversion. Treatment interruption is not considered in the definition for successful treatment (cured and treatment completed). Moreover, there remains a risk of increased relapse even after initial conversion. Also, there can be a fall & rise phenomenon that leads to declaration of successful TB treatment outcome by RNTCP definitions. However, in practice, once patient is declared as cured or treatment completed (successfully treated), they are not followed up under the programme unless they come to health system again with symptoms. Relapse is considered to be an important measure of efficacy of any treatment regimen. Hence, measuring treatment interruptions and correlating it with the long term outcome of patient is useful information for finding out reasons behind relapse and other adverse outcome (such as death) after successful treatment. Present study was conducted to assess impact of treatment irregularity on status of patients at 2 years after successful anti-TB treatment under DOTS with following objectives:

- To assess treatment interruption of New Sputum Smear Positive (NSP) Pulmonary TB patients while on treatment of the selected cohort (treated before 2 years)

- To ascertain the status of all NSP Pulmonary TB cases at 2 years after declaration of successful treatment outcome (cured or treatment completed)

- To compare unfavorable status (outcome) at 2 years after successful treatment amongst treatment interrupters as compared to non-interrupters

METHODOLOGY

Study design

It was a retrospective cohort study. Line list of all New Smear Positive (NSP) Pulmonary TB cases that were declared as cured or treatment completed between January 2009 to June 2009 was prepared from the TB registers of all TB Units from randomly selected Patan (rural) and Vadodara Municipal Corporation (urban) districts of Gujarat, India (n=706). These patients were interviewed after 24 months (±1 week) from date of declaration of successful treatment. In case of TB patients who died or not available due to some other reason, their relatives were interviewed for collecting the information. Episode of Tuberculosis in last two years was confirmed with documentary evidence.

Ethical considerations

Informed consent was taken from each participant before including them into study. For the subject observed in diseased condition during interview, referral for treatment to nearest health facility was established. Study protocol was approved from Institution Ethics Committee of BJ Medical College, Ahmedabad and administrative approval was obtained from Directorate of Health Services of Gujarat state

Data collection tools

Data was collected from RNTCP Quarterly Reports, TB registers and Patient treatment cards of each selected districts. Patients were interviewed using semi-structured questionnaire in local language after piloting. Information was collected during January to June 2011 by the field research staff recruited and trained for the study. Collected data were checked for completeness, correctness & accuracy by the field research supervisor within three days and for any missing information, data were collected by home visit by field research staff.

Data Management and Analysis

Data were coded by field research supervisor. Data entry operator created the database using EpiData entry software (Version 3.1, EpiData Association, Odense, Denmark) and entered all the coded variables by replacing patient's name

and address using unique ID. Analysis was done using EpiData Analysis software (version V2.2.2.180). Important independent variables were age, sex, occupation, history of anti-TB treatment before starting category I on diagnosed as NSP, initial grade of sputum result, extension of IP, total duration of treatment, no of missed doses in IP, no of missed doses in CP, minimum duration of any interruption, maximum duration of any interruption, mean duration of interruption. Important dependent variables were status of TB patients at 2 years after successful treatment and relapse of TB subsequent to successful treatment. Descriptive statistics were used for age, sex, socio economic status variables. Demonstration of comparability between characteristics of treatment interrupters and non-interrupters was carried out using Chi-Square and T-Test. 5% was taken as level of significance. Odds ratio for status at 2 years between treatment interrupters and non-interrupters was calculated.

Definitions

Successfully treated NSP TB Case: A TB patient with at least one initial sputum smear positive results (from Designated Microscopy Centre under RNTCP) registered in year 2008 and had completed Category I treatment regimen under DOTS and was declared cured or treatment completed as per TB registers or treatment cards

Missed dose: When a TB patient scheduled to take a dose of anti-TB medicines did not turn up to DOT center and missed that particular dose on that day but excluding doses taken on the next day on successful retrieval before next dose.

Treatment interruption: When a missed dose was not taken by the patient on subsequent day or days thus leading to non-administration of anti-TB doses for more than 1 consecutive day or leading to postponement of at least one dose, was accounted as treatment interruption.

RESULTS

Total of 706 new smear positive pulmonary TB patients were declared as successfully treated the during study period. Out of these 706 patients, data retrieval and household visits were made for 657 patients (93%).

Out of 657 patients with successful outcome studied, 326 (49.6%, 95%CI – 45.8%-53.4%) had interrupted treatment one or more times during the course of therapy. Out of those who had interrupted treatment, 95 (29.1%) patients had interrupted treatment in intensive phase, 82 (25.2%) patients had interrupted treatment in continuation phase and 149 (45.7%) patients interrupted their treatment in both phases of treatment (Table 1).

Table 1: Treatment interruption during course of therapy among patients enrolled under the study (N = 657)

	Patients (%)
Treatment interruption	
Yes	326 (49.6)
No	331 (50.4)
Treatment Interruption in different phases of treatment (N = 326)	
Intensive Phase	95 (29.1)
Continuation Phase	82 (25.2)
Both	149 (45.7)

Average number of doses missed during intensive phase and continuation phase was 7.5 and 11.9 respectively. Minimum duration of any interruption was 3.1 days, maximum duration of any interruption was 13.1 days and average duration of any interruption was 6.5 days (95%CI - 5.8-7.2). The phase wise duration of interruptions are given in table 2.

Table 2: Quantification of treatment interruption in different phases of treatment under RNTCP (N=326)

	Intensive Phase (N=259)		Continuation Phase (N=268)	
	Mean	**(95% CI)**	**Mean**	**(95% CI)**
Missed doses in IP	7.5	(6.4-8.6)	11.9	(10.1-13.6)
Minimum duration of any interruption	3.9	(3.1-4.6)	4.5	(3.9-5.2)
Maximum duration of any interruption	8.5	(7.4-9.6)	11.8	(10.4-13.2)
Mean duration of interruption	5.7	(4.9-6.6)	7.2	(6.4-7.9)

Table 3 shows comparison of proportion of treatment interruption and non-interruption, stratified by characteristics of patients. Proportion of treatment interrupters was higher in urban district (Vadodara Municipal Corporation) (65.2%, 95% CI – 60.3%-69.8%) as compared to the rural district (Patan) (27.6%, 95% CI – 22.5%-33.1%) The difference was statistically significant (p<0.01). Other parameters like age, sex, initial grading of sputum results and past history of anti-tb drugs were not significantly associated with treatment interruption.

Table 3: Comparison of proportion of treatment interruption and non-interruption, stratified by characteristics of patients

	Treatment Interruption		Total	P value
	Yes (%)	No (%)		
District				
Urban	251 (65.2)	134 (34.8)	385	<0.001
Rural	75 (27.6)	197 (72.4)	272	
Age groups				
0-14	2 (66.7)	1 (33.3)	3	0.19
15-24	78 (51.0)	75 (49.0)	153	
25-34	76 (51.4)	72 (48.6)	148	
35-44	84 (55.3)	68 (44.7)	152	
45-54	52 (45.2)	63 (54.8)	115	
55-64	22 (42.3)	30 (57.7)	52	
≥65	12 (35.3)	22 (64.7)	34	
Gender				
Male	252 (51.0)	242 (49.0)	494	0.21
Female	74 (45.4)	89 (54.6)	163	
History of anti-TB treatment				
Yes	7 (77.8)	2 (22.2)	9	0.10
No	319 (49.2)	329 (50.8)	648	
Initial grade of sputum results				
Scanty	21 (43.8)	27 (56.2)	48	0.07
1	126 (51.6)	118 (48.4)	244	
2	68 (42)	94 (58)	162	
3	111 (54.7)	92 (45.3)	203	

Table 4: Unfavorable outcome among patient with treatment interruption and without treatment interruption

	Treatment Interruption		Total (%)	OR	(95% CI)
	Yes (%)	No (%)			
Unfavourable Outcome					
Yes	50 (15.3)	38 (11.5)	88 (13.4)	1.40	(0.87-2.25)
No	276 (84.7)	293 (88.5)	569 (86.6)	1.00	
Relapse					
Yes	42 (12.9)	29 (8.8)	71 (10.8)	1.54	(0.91-2.62)
No	284 (87.1)	302 (91.2)	586 (86.6)	1.00	
Death					
Yes	25 (7.7)	14 (4.2)	39 (5.9)	1.88	(0.92-3.89)
No	301 (92.3)	317 (95.8)	618 (94.1)	1.00	
Total	326	331	657		

On analyzing status of patients at 2 years after their successful treatment, it was found that 88 (13.4%) patients either relapsed or died due to TB. Cases of these unfavourable outcomes were more (15.3%) among patients who had interruption during treatment than those without interruption during their course of therapy (11.3%) However, the observed difference was not statistically significant (OR – 1.4, 95%CI - 0.8-2.2) (Table 4). Out of 657 study subject, 71 (10.8%)

patients had relapse of TB. Though proportion of relapse was higher among treatment interrupters (12.9%) than among treatment non-interrupters (8.8%), the difference was not statistically significant (OR-1.5, 95%CI-0.9-2.6). After successful treatment of TB, 79 (12%) patients died. Death attributable to TB was 5.93% (n=39). Death rate among treatment interrupters was 7.7% in comparison to 4.2% among treatment non-interrupters, albeit the difference in the death rate was not statistically significant (OR-1.88, 95%CI-0.9-3.8).

DISCUSSION

The present study observed two important aspects of TB treatment strategy followed under RNTCP i.e. treatment interruptions during course of six or eight months of therapy and long term outcome of patients treated successfully under DOTS. In the present study, 49.6% of patients interrupted treatment during course of therapy. Kendel TR et al[5] found 47.5% treatment interruption in their study conducted in the Eastern Cape Town Provinces. Another study conducted in Russia by Jakubowiak W et al[6] found proportion of interruption to be 36% in intensive phase and 45% in continuation phase.

In the present study, it was observed that a substantial proportion (15.3%) of patients died or relapsed after being successfully treated for TB. The observed proportion of unfavourable status was similar to the combined relapse and death rate of 15% among TB patients treated with 8-months of therapy in a study conducted in Vietnam[7]. Similar findings were observed by Sophia et al. after two and half year follow up of new smear positive patients treated under RNTCP[8].

Overall 10.8% relapse rate was observed in present study. Sophia et al found relapse rate of 11.4% on two and half years follow up of new smear positive patient treated under RNTCP in city of Bangalore in India[8]. A systematic review conducted to asses long term efficacy of DOTS regimens for TB revealed wide variation in recurrence after successful treatment, ranging from 0 to 14% among 16 studies included in the review.[9] Thomas A et al[10] found the relapse rate of 12.3% in the study conducted in Tiruvallur district of South India. Cox H et al[11] found 17% of relapse rate among new sputum positive patients in their study conducted from four districts in Karkalpakstan in Uzbekistan in 2002.

Vree M et al[7] in their study among successfully treated patients in Vietnam found relapse rate of 8.6%. The relapse rate observed in the present study is higher than studies conducted around the world[9,15]. Internationally, relapse rate of more than 5% is unacceptable with questionable efficacy of regimen used to treat new cases.

Relapse rate was found to be more among treatment interrupters (12.9%) than among non-interrupters (8.8%). However, the Odds Ratio (OR) of 1.54 (95%CI 0.91-2.62), which means that the difference in relapse between interrupters and non-interrupters is not statistically significant. Relapse rate which is a long term outcome of the TB treatment is also the indicator of efficacy of the regimen. Cox et al.[9] documented inadequate treatment regimen as one of the potential contributors to recurrent TB along with other factors. Overall high relapse rate with the currently used intermittent regimen under RNTCP is sufficiently questioned for its efficacy in terms of long term success i.e relapse free cure.

Death due to TB was another unfavorable outcome analyzed in the study. The study reports TB mortality rate of 5.9% which is comparable to results of studies conducted in DOTS Programme from South India[13] and Maxico[14]. Another study conducted in Southern Ethiopia reported death rate of 7.7% (95%CI 5.2-10.2) among NSP patient followed after successful treatment.[15]

Limitations of the study: Retrospective cohort study design has implied drop-outs due to migration. Recall bias is inevitable for subsequent episodes of TB.

Implication of the study: The findings of present study necessitate review of intermittent regimen under RNTCP as it gives high unfavourable long-term outcomes. This study will provide assistance to TB Control Programme Managers for planning of interventions to address long-term unfavorable outcomes of TB treatment i.e. relapse and death. Also, the results will help in further advocacy for attending the adherence part of anti-TB treatment under RNTCP.

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