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To determine the treatment outcome in pulmonary tuberculosis patients who are detected Rifampicin Sensitive by Cartridge Based Nucleic Acid Amplification Test (CBNAAT)

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Abstract

***Background & objectives*:** India has the highest burden of tuberculosis in the world both in terms of drug sensitive and drug resistant TB and has a large impact on our economy. If we want to ensure control of the current situation with increasing numbers of resistant TB in the community, we need to ensure that the treatment regimens being given to our tuberculosis patients are efficient enough to control disease and thus avoid emergence of resistance. It has been noted that regimen for previously treated cases has a comparatively poor treatment outcome. This regimen is also against the basic principles of tuberculosis chemotherapy which says a single drug should not be added to a failing regimen. Hence, this study was planned to determine the treatment outcome in rifampicin sensitive patients which rules out the presence of resistance as the cause of decreased cure rates, and can thus effectively evaluate the effectiveness of the current regimens being provided to the tuberculosis patients under RNTCP.

***Methods*:** A prospective study was conducted at the Chest and TB hospital, Amritsar which included 100 patients diagnosed with sputum smear positive and rifampicin sensitive pulmonary tuberculosis. Treatment outcome was recorded at the completion of treatment as per the RNTCP guidelines for all patients. Treatment outcome was compared between new and previously treated cases and also its association with various other variables was seen.

***Results*:** Out of 100 study population, 27 were new cases and 73 were previously treated.Out of the 73 retreatment patients, 42(57.5%) were recurrent, 20(27.4%) were lost to follow up and 11(15.1%) were failure.14.8% of DOTS category I patient had unfavourable outcome whereas 38.4% of DOTS category II patients had unfavourable outcome and this difference came out to be significant ($p< 0.05$).

Keywords: Tuberculosis; DOTS; New cases; Retreatment cases; CBNAAT; MDR TB.

Introduction

Tuberculosis(TB) is still a worldwide public health problem inspiteof the fact that the causative organism was discovered more than 100 years ago.[1] It causes ill-health in millions of people each year and in 2015, was one of the top 10 causes of death worldwide, ranking above HIV/AIDS as one of the leading causes of death from an infectious disease.[2] This is despite the fact that most people who develop TB disease can be curedwith a timely diagnosis and correct treatment. India has the highest burden of both TB and MDR TB. India accounts for one fourth of the global burden of TB. In 2015, an estimated 28 lakh cases occurred and 4.8 lakh people died due to TB.[2]

RNTCP recommends category I for new cases which has four drugs (Rifampicin, Isoniazid, Pyrazinamide and Ethambutol) given for 6 months and Category II for previously treated cases which adds streptomycin to the category I regimen, given for 8 months.

The DOTS regimen for new cases was recommended based on the results of randomized trials. This regimen was found to have good bactericidal and good sterilizing property with low relapse rates of 0–2%. Unlike the category I, the category II retreatment regimen was a product of expert opinion.[3]It was originally designed for resource-poor settings with low prevalence of initial drug resistance, and for patients previously treated with a regimen that used rifampicin only for the first two months of therapy.[4]However, this regimen was increasingly criticized[5]because of poor results, particularly in settings where rifampicin was used throughout initial therapy or prevalence of initial drug resistance was high.[6,7]When used after failure of category I treatment, this regimen effectively allowed addition of streptomycin to the category I regimen i.e. addition of one drug to a failing regimen, which was against the basic principles of chemotherapy for tuberculosis.

Drug resistance in tuberculosis develops by the selective growth of resistant mutants.[8] MDR-TB is a man-made phenomenon in which poor treatment, poor drugs, and poor adherence has lead to the development of MDR-TB.[9]

Thus, it is important to know the effectiveness of the regimen on which a pulmonary tuberculosis patient is put and to ensure that the chances of such patients getting cured via this regimen is high. Hence, this study was planned to determine the treatment outcome in rifampicin sensitive patients which rules out the presence of resistance as the cause of decreased cure rates, and can thus effectively evaluate the effectiveness of the current regimens being provided to the tuberculosis patients under RNTCP.

Materials and Methods

This study was conducted after approval from the institution's ethical committee. This was an observational prospective study which was carried out in the Department of Chest and Tuberculosis, Government Medical College, Amritsar. The study included 100 patients diagnosed with sputum smear positive pulmonary tuberculosis and who were detected Rifampicin-sensitive by CBNAAT, who came to outpatient department or were admitted in wards over a period of 18 months. The approval of institutional thesis and ethics committee was taken before the start of study. Participants who met the inclusion criteria were recruited after giving information regarding the study in their vernacular language and written informed consent was obtained.

Inclusion Criteria:

1. Patients having sputum smear positive pulmonary tuberculosis.
2. Cases having Rifampicin sensitivity as detected by CBNAAT.
3. Patients initiated on DOTS Regimen.

Exclusion Criteria:

1. Sputum smear negative pulmonary tuberculosis patients.
2. Patients having extra-pulmonary tuberculosis.
3. Drug resistant pulmonary tuberculosis patients.

A pre-structured proforma was filled in those cases which were included in the study including history, general physical and respiratory examination,contact history, past history of ATT(anti-tubercular therapy) intake, history of any addiction, CBC, RBS,HIV, Sputum smear at initiation of treatment, at end of IP and at completion of treatment, chest X-ray findings, etc.

The enrolled patients were then categorized as New cases, Recurrent TB cases,Treatment After failure cases, and Treatment after loss to follow-up; according to the RNTCP definitions. These patients were given DOTS according to the RNTCP guidelines: Category I to new patients and Category II to the previously treated cases.

Treatment outcome in all these patients were recorded according to the RNTCP guidelines as Cured, Treatment completed, Failure, Lost to follow up, Treatment Regimen Changed or Died.

Cured and Treatment completion were considered as favourable treatment outcomes and loss to follow-up, failure, treatment regimen changed and deaths were considered as unfavorable treatment outcomes.Association of various variables with treatment outcome was assessed using a Chi-square test.P values of <0.05 were considered to indicate statistical significance.

Results

This study included 100 patients diagnosed with sputum smear positive pulmonary tuberculosis and who were detected Rifampicin-sensitive by CBNAAT. In our study, maximum patients were present in age group 21 – 30 years i.e. 25%, followed by 24 % in age group 41-50 years. Minimum patients were in age group > 60 years. 69% of the study group were in the age group 20 – 50 years. Treatment outcome in each age group was as follows:

Table 1:Association of age with treatment outcome

Age (yrs)	Outcome	
	Unfavourable	Favourable
<20	4 (22.2%)	14 (77.8%)
21-30	9 (36.0%)	16 (64.0%)
31-40	6 (30.0%)	14 (70.0%)
41-50	10 (41.7%)	14 (58.3%)
51-60	2 (20.0%)	8 (80.0%)
>60	1 (33.3%)	2 (66.7%)

Age did not have a significant association with outcome.(X^2=2.706; df=5; p>0.05)

Maximum patients in our study were male i.e. 69% and the Male : Female ratio came out to be 2.2:1. 74.2% of females whereas 65.2% of males had favourable outcome but this difference was not statistically significant.

The most common addiction in our study population was alcoholism, present in 55% of study subjects. It was followed by smoking which was present in 22% patients and drug abuse was present in 16% of cases. It did not have any significant association with the outcome of the patients.

There were 19 cases who were diabetic. Among diabetics, 63.2% had a favourable outcome and among non-diabetics, 69.1% had a favourable outcome, but this difference was also not statistically significant.

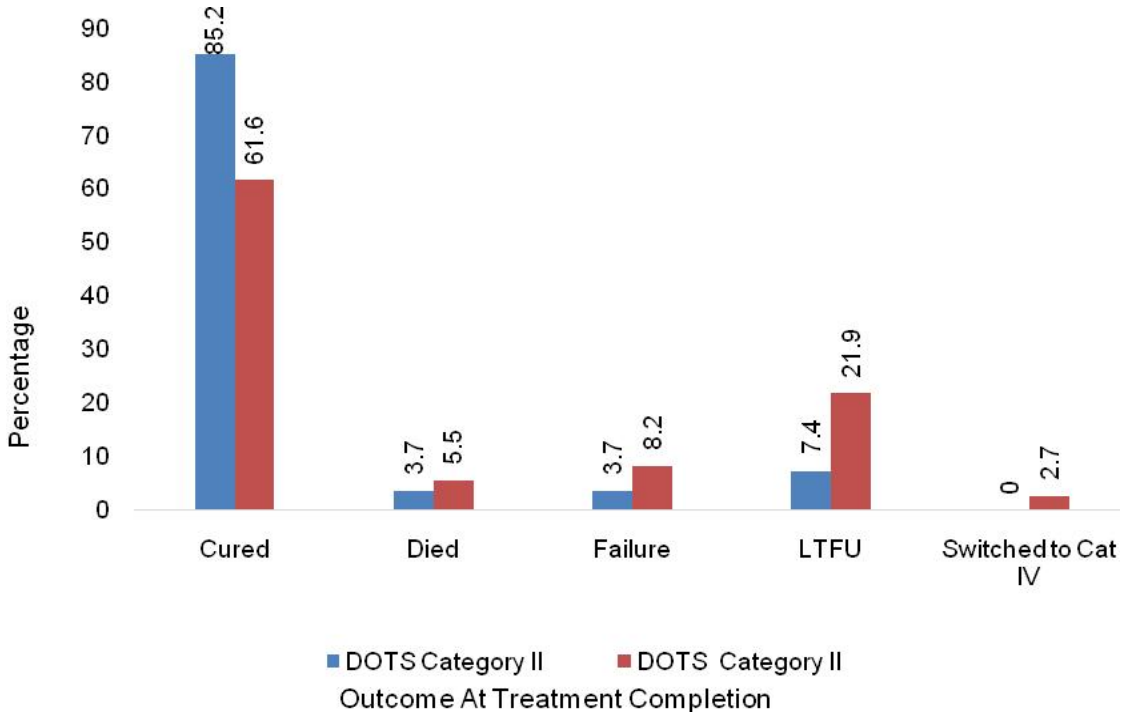
Among the 100 enrolled cases, 27 were new cases and 73 were previously treated or ‘retreatment’ cases. Out of the 73 retreatment patients, maximum i.e. 42 (57.5%) were under the category ‘recurrent tuberculosis’, followed by ‘treatment after lost to follow up’ which had 20 patients i.e. 27.4%. 11 (15.1%) were under the category ‘treatment after failure’.

Out of the 27 new sputum smear positive patients, 23 (85.2%) were cured, 1 had died (3.7%), failure rate was 3.7% and 2 patients i.e. 7.4% were lost to follow up. The treatment outcome in previously treated category of patients was as follows:

Table 2:Treatment outcome in previously treated pulmonary tuberculosis patients

Type of patient / Treatment Outcome	Failure	Loss to follow up	Recurrent	Total
Cured/ Treatment Completed	5 (45.4%)	10 (50.0%)	30 (71.4%)	45 (61.6%)
Died	1 (9.1%)	1 (5.0%)	2 (4.7%)	4 (5.4%)
Failure	1 (9.1%)	4 (20%)	2 (4.7%)	7 (9.6%)
LTFU	3 (27.3%)	5 (25.0%)	7 (16.7%)	15 (20.5%)
Switched to Cat IV	1 (9.1%)	0 (0.0%)	1 (2.4%)	2 (2.7%)
Total	11	20	42	73

Treatment Outcome was calculated for patients taking DOTS category I and DOTS category II separately:



We compared the treatment outcome for patients taking DOTS category I and Category II and the results were:

Table 3: Comparison of favourable and unfavourable outcome depending on the dots category initiated

	Unfavourable Outcome	Favourable Outcome	Total
Dots Category I	4 (14.8%)	23 (85.2%)	27 (100%)
Dots Category II	28(38.4%)	45 (61.6%)	73 (100%)
Total	32	68	100

As shown in the above table, 14.8% of DOTS category I patients had unfavourable outcome whereas 38.4% of DOTS category II patients had unfavourable outcome and this difference came out to be significant (χ^2=5·020, df = 1, p =.025).

Discussion

Tuberculosis kills more people in India than any other infectious disease. In India, every day more than 6000 people develop this disease and more than 600 people die of tuberculosis (i.e. 2 deaths every 5 minutes).[10]

The occurrence of resistant forms of TB has increased significantly since the 1980s.[11]An estimated 1.3 lakh incident multi-drug resistant TB patients emerge annually in India which includes 79000 MDR-TB patients among notified pulmonary cases.[12]Appropriatetreatment to all tuberculosis patients is a pre-requisite to the prevention of emergence of resistance. The outcome of "careless care"[13]over time has resulted in progressive resistance to the anti-TB drugs.

Poor chemotherapy in the form of inadequate drug doses,inadequate drugs or addition of a single drug to a failing regimen (which is also called addition syndrome) results in selective growth of the drug-resistant mutants and consequently acquired drug-resistant TB from multiplication of such bacilli. Contacts of such resistant cases develop primary drug-resistant TB.[14]Thus, drug resistance in tuberculosis is a "man-made problem"; acquired resistance, a mark of a poor treatment practices in the current time and primary resistance, an indicator of treatment practices in the past.[15]

Treatment outcomes of previously treated smear positive pulmonary tuberculosis patients have remained poor in India as well as globally. Recent studies have also queried the utility of using the standard Category II regimen in re-treatment TB patients, especially in patients who failed a Category I regimen.[5,6]

It thus becomes important for researchers to know the extent to which the patients initially put on anti-tubercular therapy are really benefiting from the treatment on its completion and the role of influencing factors in this aspect.

Our study showed that a large number of patients being treated on DOTS had an unfavourable outcome and that retreatment patients(38.4%) had significantly poorer treatment outcome as compared to new cases(14.8%). This is similar to the results of previous studies as done by Pardeshi et al[16] in which a comparison of the treatment outcome showed that the chances of a favourable outcome were significantly less in the re-treatment group (66.47%) than in the new smear positive group (84.28%); or the study done by Joseph et al[17], in which comparison in the treatment outcomes between NSP and retreatment groups showed that chances of a favourable outcome were significantly less in the retreatment group (47.3%) than in the NSP group (77.4%).

This highlights the importance of ensuring the successful completion of treatment among patients with TB who are put on Category I regimen to prevent them from entering a Category II treatment regimen. Also, there is need for more studies to determine the efficacy of DOTS category II as treatment regimen for previously treated cases.

Conclusion

The current scenario with increasing cases of MDR and XDR TB in India is really a matter of concern. If the situation is not controlled soon, we are not far from landing in a situation similar to the "pre-antibiotic era" with no effective drug left sensitive for the TB bacillus. With very few new drugs becoming available for the treatment of drug resistant TB, the need of the hour is to use the existing drugs effectively as per the basic principles of chemotherapy and to ensure a really effective regimen being given to all the tuberculosis patients, before it is too late.

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