Original Research Article

Evaluation of effectiveness of category – II regimen under revised national tuberculosis control programme

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Abstract

Background: Tuberculosis is an infectious disease caused by a bacillus – Mycobacterium Tuberculosis – That Spreads Through the air when untreated TB patients cough. **Aims and Objectives:** To assess the treatment outcome among culture positive retreatment cases treated under category II regimen, in correlation with pre- treatment and post treatment mycobacterial drug sensitivity. **Materials and Methods:** The study was conducted in the department of pulmonology, Asram Hospital, Elluru. Pulmonology Unit, Asram hospital started its activities in April 2012, catering to the needs of 4.41 lakh population residing within its limits Elluru. All the smear positive pulmonary tuberculosis retreatment patients registered for treatment under RNTCP and initiated on cat – II regimen in this centre, from Oct'2017 to Dec' 2018, formed the study group. **Results:** During the period between oct 2017anddec 2018, a total of 48 retreatment patients were registered in the TB unit, Asram hospital, eluru and 36 (75%) who were culture positive among them formed the study group. Of these 26 (63%) were males and 10(27%) females **Conclusions:** The mean age of presentation of cat II patients at T.B. unit of SVRRGGH is 42.63 + 11.81 (Mean±S.D) years. Fibrocavitory lesions on chest X-ray was the most common finding. Treatment after default cases constituted the bulk of the study group (75%). All the treatment failure cases were resistant to two or more drugs before initiation of cat II regimen.
Key Word: revised national tuberculosis control programme.

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INTRODUCTION

Tuberculosis is an infectious disease caused by a bacillus – Mycobacterium Tuberculosis – That Spreads Through the air when untreated TB patients cough[1]. Tuberculosis, still remains a major public health problem in most of the developing countries including India. The reasons are many ranging from poor socio economic and nutritional status, crowded living conditions, inadequately managed as well as ill focussed, national tuberculosis programmes put into operation, emergence of multi drug resistant mycobacteria and the global epidemic of human immunodeficiency .Nearly one third of the Global population i.e. two billion people is infected with *Mycobacterium Tuberculosis* and at risk of developing the disease. More than eight million people develop active TB every year and about two million die. India, China and Indonesia account for half of the total TB case mortality[2]. More than 90% of global TB cases and deaths occur in the developing world, where 75% of the cases are in the most economically productive age group (15–54 years)[3]. Coinfection with Human immuno deficiency virus (HIV) significantly increases the risk of developing TB[4].

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MATERIALS AND METHODS

The study was conducted in the department of pulmonology, Asram Hospital, Eluru. Pulmonology Unit, Asram hospital started its activities in April 2012, catering to the needs of 4.41 lakh population residing within its limits elluru. All the smear positive pulmonary tuberculosis retreatment patients registered for treatment under RNTCP and initiated on cat – II regimen in this centre, from Oct'2017 to Dec' 2018, formed the study group. All these patients were evaluated with detailed history and physical examination. The cat- II regimen (2(SEHRZ)3/1 (EHRZ)3/5(HER)3) was administered under direct observation of each dose in the intensive phase, followed by supervised administration of the first weekly dose of continuation phase and the remaining two doses issued for self administration. Two pretreatment sputum specimens were collected from each patient before initiation of treatment and two follow-up sputum specimens were obtained as per RNTCP guidelines at the end of 5 months and 8 months (32). The specimens were immediately transported. The specimens were immediately transported to the Dept. of Microbiology, Asram medical college for Microscopy for Culture and Susceptibility Tests. On arrival in the laboratory the sputum specimens were homogenized with a mucolytic agent (N acetyl – L– Cysteine) and decontaminant (2% NAOH Sol) to render the bacterial contaminants nonviable (Lyfectol, Tulip Diagnostics). After decontamination sputum is centrifuged at 3000 rpm for 20 minutes and sediment thus obtained is used for AFB staining and culture. Specimens were inoculated onto standardized LJ Media slants (HI media laboratories) containing all the first line anti-tuberculosis drugs and two controls. The cultures were incubated at 37®c, read after two weeks for growth, every week for a total of 8 weeks.

Bacteriological Investigations: Laboratory investigations were (a) smear microscopy with ZiehlNeelsen technique as per RNTCP Guide lines. Culture using Lowenstein Jensen (LJ) medium and susceptibility testing with critical drug concentrations for INH 0.2 g / ml,rifampicin 40 g/ ml, Streptomycin 4 g/ml, ethambutol 2 g /ml and pyrazinamide – 200 g/ml at PH 5.5. Growth on slants containing antituberculosis drugs indicates resistant organisms. The Niacin and Nitrate Reduction tests were carried out for mycobacterial identification[5].

Data collection: Information was obtained on the history of previous TB treatment, number of treatment episodes, with doses, duration and treatment source. Medical records pertaining to previous treatment if available, too were scrutinized. Utmost care was taken to eliminate new cases. Information was also obtained on the socio demographic profile of patients knowledge about the disease. The definitions of type of patients (Relapse, treatment after default, failure, others) were according to the criteria laid down under RNTCP[6]. However the definitions for treatment outcome as "Cure" and failure were based on the culture results[7]. When final culture was reported as contaminated the outcome was considered as treatment completed if the prescribed duration of treatment had been completed. Cure and treatment completed were considered as favourable while failure, death and default were unfavourable outcomes.

Statistical Analysis: The differences between proportions were tested by applying Chi-square test after yates correction, using Epi-info software. P value of less than 0.05 were considered to indicate statistical significance. Difference between sub groups was expressed as 95% confidence intervals. In cases where the expected value in any cell is less than 5, Fishers Exact test (two-tailed) was employed.

RESULTS

During the period between oct 2017anddec 2018, a total of 48 retreatment patients were registered in the TB unit, Asram hospital, Eluru and 36 (75%) who were culture positive among them formed the study group. Of these 26 (63%) were males and 10(27%) females (Table 1)

Table 1: Age and sex distribution of patients

Age group (years)	Male	Female	Total
20 – 39	8 (57.2)	6 (42.8)	14 (38.9)
40 – 59	15 (83.3)	3 (16.7)	18 (50.0)
> 60	3 (75.0)	1 (25.0)	4 (11.1)
Total	**26 (63%)**	**10 (27%)**	**36**

Figures in parenthesis represent percentages. X2 = 1.51 Mean = 42.63±11.81 df = 1 (mean±S.D) P = 0.14 Distribution of study group, A total of 48 retreatment patients were registered and 36 (75%) who were culture positive among them formed the study group, of these 19 (52.8%) were initially susceptible to all the drugs (Fig1). Of the study group, 24 (66.6%) treatment after default cases constituted the majority, with median duration of prior TB treatment of 12 weeks and 14 (58.3%) were pretreatment susceptible to all drugs. All treatment failure cases were resistant to two or more drugs compared to rest of the group (P<0.001).

Pretreatment Drug Resistance: Pretreatment drug resistance, either alone or in combination with other drugs was highest to Isoniazid (H) (44.5%) followed by streptomycin (S) (36.2%) and Rifampicin (R) (16.6%). The proportion with MDR TB (resistance to H, R with or without resistance to others) was 16.6%. In the pre-treatment resistant group 9(53.0%) had history of > 20 weeks prior TB treatment compared to 7 (37%) in pre-treatment susceptible group (P = 0.33).

Table 2: Pretreatment Drug Resistance Pattern Among Cat II Patients

Resistance status	Number	Percentage	95% C.I
Susceptible to all	19	52.8%	36.5-69.1
Resistant to at least one drug	17	47.2%	30.9-63.5
One drug only	5	13.9%	2.6-25.2
S	1	2.78%	0.0-8.15
H	4	11.12	0.86-21.4
Two drugs only	6	16.6%	4.4-28.7
H,.S	6	16.6%	4.4-28.7
Three or more drugs	6	16.6%	4.4-28.7
H,R,S	6	16.6%	4.4-28.7
At least one drug			
S	13	36.2%	20.5-52.2
H	16	44.5%	28.3-60.7
R	6	16.6%	4.4-28.7
MDR	6	16.6%	4.4-28.7

Treatment Outcome: The overall favourable treatment outcome among category – II patients was 58.3% (cure 38.8%, treatment completion 19.4%). The unfavourable treatment outcome was in 41.7% of patients, of these 19.4% defaulted (Table: 2). The favourable outcome was in 78.9% in pre-treatment drug usceptible group compared to 35.3% in the resistant group (p=0.02). Failure of treatment was significantly more frequent with the pre treatment drug resistant group (35.3%) compared to pre-treatment susceptible group (p < 0.001). Mortality (death) among retreatment cases was 5.5%.

DISCUSSION

Drug resistant tuberculosis and particularly multidrug resistant tuberculosis (MDR-TB, defined as resistance to at least Isoniazid and rifampicin) is an increasing health problem and a serious challenge to TB control programmes[8, 9, 10]. Poor or suboptimal TB control programmes can lead to rapid emergence of drug resistance especially if the prevalence of tuberculosis is high in that region[11, 12]. As drug resistance is a man made phenomenon and is usually due to inadequate treatment, such resistance may be a useful indicator for monitoring the efficiency of tuberculosis control programmes[13]. Studies have shown that prior but ineffective treatment is a strong predictor of drug resistance[14, 15] According to the recommendations of International union against tuberculosis and lung diseases (IUATLD) and the world health organization (WHO) previously treated tuberculosis patients are offered standardised retreatment. Half of the patients (50.0%) in the study were between 40 and60 years of age. Mean age at presentation was 42.63 (Range = 22-60 years). Age wise distribution of patients showed a peak in 4th and 5th decades. This peak was more pronounced in males in whom 83% of the patients were between 40 and 60 years (p=0.14) though it is not statistically significant due to small sample size. The male female ratio among retreatment cases during the study period was 2.6. The male predominance noted in the present study has also been observed in two other previous studies[16, 17] of the total 48 retreatment cases culture for mycobacterium tuberculosis was positive in 36 patients (75%). In a similar study by sophiavijay *et al*. Culture was positive in 84.3% of retreatment cases[22] more than half of the study group (52.8%) were initially susceptible to all the regimen drugs. Study done by sophiavijay *et al*. in Banglore reported that more than 60% of the study group were initially susceptible to all the drugs[22]. In the present study 47.2% of the all patients were resistant to one or more drugs. Clinically, cough with expectoration and fever were the most common presenting complaints in 90% of patients, followed by breathlessness (60%), loss of appetite (55%) and haemoptysis (25%). Radiologically majority (80%) of patients showed moderately advanced fibrocavitary disease on chest X-ray, where as in remaining 20% bilateral pulmonary infiltrates were demonstrable. The existence of a pulmonary cavitary lesion has been observed to be predisposing to the development of drug resistance in a study in turkey by OguzKarabay *et al*[18] and in south California by Ben-dov I, *et al*.[19].

Though in the present study no such association of statistical significance was noted. Also studies by Fischle *et al*[20], and frieden *et al*[21] did not find that cavitary lesion was a risk factor for development of resistance. Treatment after default cases constituted the majority (66.6%) in the study group. Similar observation was noted in two other studies done in Bangalore India (65.5%) [22] and cotonou, Benin(47.8%) [58]. Relapse patients constituted 25% of the study group. The majority of relapses (6 out of 9) occurred in the year following treatment completion as did treatment after default patients (18 out of 24). This is in line with the study done to assess the retreatment outcome in cotonou, Benin[58]. Only 3 were treatment failures in the entire study group, and all the three cases were pretreatment resistant to two or more drugs (p=0.0001). In one study in peruJ. C. Saravia *et al*[77]showed that 88% of patients has isolates demonstrating resistance to both INH and rifampicin (MDR-TB) before initiating category II regimen in treatment failure cases. This high rate of MDR TB is alarming and WHO in its most recent guidelines indicated the importance of alternatives to category II when category I failures are highly likely to have MDR-TB [23]. Pre- treatment drug resistance pattern among category II patients in the present study either alone or in combination with other drugs demonstrated highest resistance to Isoniazid (44.5%) which was also shown in

previous studies,[22, 23] followed by streptomycin (36.2%) and rifampicin (16.6%). Isolated resistance to one drug was found only for Isoniazid and streptomycin. Initial streptomycin resistance of 36.2% in the present study could be due to the cycling of failing patient with drug resistant disease through the ineffective category-II regimen, where they acquired further resistance to streptomycin and infected others with these highly resistant strains. Similar results were observation in a study in Peru[77]. Resistance to Isoniazid of 44.5% in the present study is much higher when compared to previous studies in Bangalore where a 27.4% of category II patients were resistant to INH. This difference may be due to small sample size of present study. The proportion with multidrug resistant tuberculosis in the present study was 16.6%. The median prevalence of acquired MDR TB was 13.0% with a range of O percent (Kenya) to 54.4% (Latvia) in the report by WHO-IUATLD global project on Anti-tuberculosis drug resistance surveillance between 1994-1997[68]. In this study resistance to anti-tuberculosis drugs was found in all 35 countries surveyed suggesting that it is a global problem. In a study conducted in Gujarat in previously treated tuberculosis patients MDR TB was noted in 35.2%[69]. Reliable data on the epidemiology of MDR-TB are lacking from India[70]. A prevalence of 12.8% MDR TB was observed in previous study on outcome of retreatment patients by sophiavijay *et al.*[22] The rate of acquired MDR (27.6%) was noted to be high in a study from cameroon[29] whereas study from Poland[30] showed only 7% of strains in previously treated patients to be MDR. In the present study 53% of patients in the pretreatment resistant group had history of > 20 weeks prior TB treatment compared to 37% in pre treatment susceptible group (p = 0.33) although this finding is not statistically significant due to small sample size. The overall favourable treatment outcome in the present study was 58.3% with a cure rate of 38.8% and the remaining 19.4% of patients completed treatment. The overall favourable outcome observed in a study in Bangalore, India was only 39.8%[22] as a result of high proportion of defaults (43.8%) In contrast a cure rate of 78% was noted in other study done on retreatment patients at Cotonou, Benin. Another striking difference in this study was 85% cure rate in failure cases and only 59% in defaults[58]. The cat II treatment outcome in other countries is also low (Azerbaizan 64% Armenia 45% Georgia 35%) In the present study statistically significant favourable outcome was observed (78.9) in pre treatment susceptible group compared to (35.3%) the resistant group (p=0.02) Another significant finding in the present study was, a failure rate of 35.3% among the pretreatment resistant group while there were no failures in the susceptible group (p<0.001). Both these findings are in line with study done by Sophia Vijay *et al.*[22] The mortality rate in the present study was 5.5% while it was 3.1% in another study done in India, 13% in a study done at Cotonon, Benin. A study from Orissa also showed a mortality rate of 12.3% during retreatment with category II regimen[31]. Both the patients who died in the present study were in the pretreatment resistant group and were harbouring multidrug resistant bacilli (Resistant to H, R and S). The cause of death in one patient was massive haemoptysis with aspiration asphyxia and the cause in other patient was not known. Majority (76.4%) of the pre treatment susceptible group of patients became culture negative and 3 out of 4 culture positives were still susceptible at the time of final interview. This observation was similar to the one noted by Sophia Vijay *et al*[22] indicating a good treatment outcome among default and relapse cases who were put on cat II treatment Other studies from abroad also showed similar results[59, 32]. On the other hand in the 15 pre treatment resistant group, a significantly lower proportion 4(26.6%) became culture negative which was statistically significant (p=0.013) and of the 11 who remained culture positive 72.7% continued to be resistant, half of whom were pre treatment MDR. These findings coincide with a growing body of evidence that category II regimens results in poor outcomes when used in category I failures[26, 47, 32, 33, 34]. When the resistant group was subdivided into MDR and non MDR, a statistically, significant favourable response was noted among non-MDR group of patients when compared to MDR group (p=0.04). After excluding defaults no favourable outcome was observed among the MDR group when compared to 54.5% among the non-MDR cases (p<0.001). Another statistically significant finding in the present study was, treatment failures among those with MDR were 66.6% compared to 18.2% in the non MDR group (p=0.04) In the present study emergence of drug resistance during treatment occurred in 15.6% among 32 patients with final culture results and majority of this patients were in pre treatment resistant group. The overall emergence of drug resistance to rifampicin during treatment in the present study was 3.125% where as it was 1.8% in the previous study by sophiavijay *et al.*[22] This seemingly high rifampicin resistance could be due to small sample size of present study. In the present study no favourable outcome was observed in failure cases when compared with other types. All the three treatment failure cases enrolled in the present study were proven to be mutidrug resistant. In addition these three cases developed resistance to ethambutol, at the completion of retreatment. This observation supports the opinion of many clinicians who are afraid of adding a single drug to a failing regimen, resulting in further acquired resistance.[55, 34]. In one study by Saravia J.E *et al.* in peru a

favourable outcome of only 15% was observed in treatment failure patients started on WHO recommended cat II retreatment regimen.[34] WHO has recently revised its policy for failure cases and recommended Individualised regimens including second line drugs in the presence of MDR TB.[23] In the present study majority of the relapse cases (67%) had favourable outcome, indicating effectiveness of category II regimen in this subset of patients. Similar results were observed in other studies on retreatment outcome.[58, 22, 34] suggesting that cat II regimen is effective for relapse cases. In the present study majority of the (70%) defaults in the study group occurred by the end of intensive phase. K.C.Chang *et al.* From Hong Kong in a study reported that majority of the defaults occurred in the continuation phase. They also reported a defaulter rate of 8.5% for retreatment cases[35]. Where as present study shows 19.4% default rate for retreatment cases which is close to 15% average default rate reported by Khatri *et al*[36] among all patients on category II regimen from 1993 to 1998 in India. That a majority of the defaults occurred by the end of intensive phase has also been reported in the earlier studies with unsupervised short course chemotherapy[37,38] warranting greater care and immediate corrective actions for successful treatment completion. Another favourable observation in the present study was most of the defaulters were culture negative for mycobacterium tuberculosis at the end of retreatment, thought it cannot be equated with cure. Present study showed better treatment adherence among women, when compared to men similar results were obtained from other studies[16, 36]. Previous studies[16, 22, 37] also showed that default rate among cat II patients was more in case of treatment after default set of patients when compared to relapses and failures. A study in New York city showed that treatment defaulters would contribute to the ongoing spread of disease and the emergence of drug resistant TB in the community[80]. K.C.Chang *et al.* From Hong Kong in their study reported that past history of tuberculosis was a risk factor for default only when there was previous default. They also showed significant association between smoking, default and undesirable treatment adherence patterns[36]. In the present study two variables viz. Pre treatment drug susceptibility (p=0.02) (Resistance to any drug) and history of prior TB treatment 20weeks (p=0.001) were found to be associated with overall unfavourable out come which was statistically significant. Oguzkarabay *et al* from Turkey[20] reported that non-compliance with treatment and a regimen of Inadequate treatment increases the chance of development of drug resistance by 10-15times. Espinal[14] *et al.* also reported that prior but ineffective treatment is a strong predictor of drug resistance. Previous TB treatment of more than 24 weeks was identified as a risk factor associated with MDR in anunivariate analysis of 111 patients in Cameroon[23]. Pleumpanupat *et al.* From Thailand[38] in their study observed that the only factor significantly associated with resistance to at least one drug and MDR TB was a history of previous tuberculosis treatment. Even in the present study patients with >24 weeks of previous TB treatment were more in the pre treatment resistant group (p=0.002). This group also had more treatment failures to cat II regimen compared to sensitive group. In a study from Saudi Arabia[39] previous history of Anti tuberculosis treatment and young age were found to be risk factors associated with development of MDR TB in a study from New Delhi[40] the presence of past history of TB, poor compliance to treatment, low socio economic status and body mass index (BMI) <18 kg/m^2 were independent contributors to the risk of developing MDR TB.

CONCLUSIONS

- The mean age of presentation of cat II patients at T.B. unit of SVRRGGH is 42.63 + 11.81 (mean±S.D) years.
- Fibrocavitory lesions on chest X-ray was the most common finding
- Treatment after default cases constituted the bulk of the study group (75%)
- All the treatment failure cases were resistant to two or more drugs before initiation of cat II regimen
- Pretreatment resistance was most commonly found to INH (36.2%) and the proportion of MDR TB was 16.6%
- The mortality rate among retreatment cases in the present study was 5.5%
- The overall favourable retreatment outcome among category - II patients was 58.3%
- No favourable outcome was observed among the MDR TB group when compared to non-MDR TB cases.
- The overall emergence of drug resistance to rifampicin was 3.125% and for ethambutol was 13.2%
- Pre treatment drug resistance was significantly associated with unfavourable outcome (p=0.02
- Duration of previous TB treatment of > 20 weeks was also significantly associated with unfavourable outcome (p=0.001
- The category II (retreatement) regimen seems to be adequate for relapse and treatment after default cases, but ineffective for treatment failure cases.

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