

Original Research Article

A CROSS SECTIONAL STUDY TO ASSESS VARIOUS FACTORS AFFECTING TREATMENT OUTCOME OF SHORTER MULTI DRUG RESISTANT TUBERCULOSIS REGIMEN AT A TERTIARY HEALTH

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Abstract:

Background: - A significant burden is multidrug or rifampicin resistant tuberculosis (MDR/RR-TB).

Poses a global danger to the prevention and eradication of TB worldwide. Since 2016, WHO recommendations have allowed for the option of treating MDR/RR-TB with a conventional regimen lasting 9 to 11 months (referred to as the "shorter regimen") as opposed to a customized regimen lasting at least 20 months. The goal of the current study was to pinpoint variables influencing how well MDR-TB patients responded to a shorter injectable-based regimen.

Objective: - To study the factors affecting the treatment outcome of shorter MDR TB regimen among patients attending M.Y. hospital (tertiary level hospital) for treatment under national tuberculosis elimination program (NTEP).

Methodology: - At M.Y. hospital (a tertiary level hospital), an ambispective observational study with 55 enrolled MDR/RR TB patients was conducted. Patients with successful outcomes and unsuccessful outcomes were evaluated and compared in terms of their demographic profiles, smoking habits, clinical histories, socioeconomic level, and histories of ATT, among other factors that could be linked to treatment outcomes. The results were drawn using a number of statistical tests, including the unpaired t test, Fisher exact test, and Chi Square test.

Results- On univariate analysis significant factors associated with unsuccessful outcome were: Underweight [BMI] (p-value-0.003), Anemia (p=<.000), Multiple courses in previous (p-value-0.001), previously h/o of ATT (p=0.035), Chest X- ray bilateral (p=0.007), regimen taken (p-value-0.019), late sputum conversion at 3 month (p-value 0.071), at 4 month (p-value 0.001), 9th month (p-value 0.000). On multiple logistic regression analysis factor which were found to be independently and significantly associated with unsuccessful outcome were Anemia (p=0.049).

Conclusion- Our study was an ambispective (combined prospective and retrospective) observational study, done in the 55 enrolled MDR/RR TB patients. The median age was 25.5. Low BMI, bilateral disease on chest x-rays, anemia, multiple ATT courses in the past, a history of multiple ATT courses, high sputum grading, not following the recommended and standard regimen, and late sputum conversion were found in our study to be significantly associated. Anemia was independently related with a worse result on a multivariate analysis.

Key words- MDR-TB, ATT, Shorter MDR regimen

1. Introduction

In 2022, an estimated 10.6 million people fell ill with tuberculosis (TB) worldwide. 5.8 million Men, 3.5 million women and 1.3 million children. A total of 1.3 million people died from TB in 2022 (including 167 000 people with HIV). Worldwide, TB is the second leading infectious killer after COVID-19 (above HIV/AIDS). Multidrug-resistant TB (MDR-TB) remains a public health crisis and a health security threat. Only about two in five people with drug resistant TB accessed treatment in 2022. Multidrug-resistant tuberculosis (MDR-TB) is a form of TB caused by bacteria that do not respond to isoniazid and rifampicin, the 2 most effective first-line anti-TB drugs. MDR-TB is treatable and curable by using second-line drugs. However, second-line treatment options are limited and require extensive chemotherapy (up to 2 years of treatment) with medicines that are expensive and toxic. (1) Worldwide in 2018, the treatment success rate of MDR/RR TB patients was 59%. In 2020, WHO recommended a new shorter (9-11 months) and fully-oral regimen for patients with MDR-TB. This research has shown that patients find it easier to complete the regimen, compared with the longer regimens that last up to 20 months. Resistance to fluoroquinolones should be excluded prior to the initiation of treatment with this regimen. (1)

2. Method and patient

Study setting

This study was conducted between January 2021 and February 2022 at M.Y. Hospital Indore after obtaining Ethical Approval from Institutional Research and Ethical Committee. This was an ambispective (combined prospective and retrospective) observational study. Patients with rifampicin resistance (RR) and MDR pulmonary TB who have attended or attending drug-resistant tuberculosis (DRTB) centres under PMDT and who had completed a shorter MDR regimen in the last year or already under shorter MDR regimen / or yet to be on shorter MDR TB regimen in next one year were included. Pregnancy, critically ill patient, any extrapulmonary disease in people living with HIV (PLHIV), intolerance to any drugs in shorter MDR TB regimen or risk of toxicity from medicine in the shorter regimen (e.g., drug-drug interactions), disseminated disease, meningeal or central nervous system TB were excluded. Drug susceptibility testing (DST) showing fluoroquinolone (FQ) or second-line injectable (SLI) resistance or the presence of InhA mutation (for Eto) or resistance to pyrazinamide (Z) were excluded. Also, if the DST (FQ, SLI, Inh A mutation and Z) was not available and there was a history of intake of these second-line drugs for more than 1 month were also excluded. All participants were explained in detail about the study and informed written consent was taken from each participant. Data and records were also analysed for the retrospective group. Patients were treated with injections containing shorter MDR-TB regimen. Cured was considered as successful outcome, while lost to follow-up (LTFU), death and regimen change were considered as unsuccessful outcome.

Shorter MDR-TB regimen Following the intensive phase of 4 to 6 months of amikacin, moxifloxacin (high dose), ethionamide, isoniazid (high dose), clofazimine, pyrazinamide, and ethambutol, patients underwent a continuation phase of 5 months of moxifloxacin (high dose), clofazimine, pyrazinamide, and ethambutol. Intensive phase could be extended to 5-6 months in case of delayed conversion [4].

Study sample size

The study enrolled all the patients with rifampicin resistance, and MDR-pulmonary TB with age ≥ 18 years meeting the inclusion criteria. According to Shorter MDR Bangladesh regimen [5], prevalence of favourable outcome is 82%, hence $P=0.82$.

$$\begin{aligned} \text{Hence sample size } N &= \frac{(Z_{\alpha/2})^2 \times P \times (1-P)}{E^2} \\ &= \frac{(1.96)^2 \times 0.82 \times (1-0.82)}{(0.05)^2} \\ &= 227 \end{aligned}$$

N = Sample size, total no. of smear positive cases registered in the previous year area to be studied

$Z_{\alpha/2}$ = Z Statistic at 95% confidence interval = 1.96

P = Prevalence

E = Precision assumed to be 0.05

However, in our institute last year only 65 patients were put on shorter MDR TB regimen, hence we applied the finite population correction to the sample-

$$n_0 = \frac{n \times N}{n + (N-1)} \quad \text{where } n=65, N=227$$

$$\begin{aligned} &= \frac{65 \times 227}{65 + (227-1)} \\ &= 50.72 \approx 51 = \text{New sample size} \end{aligned}$$

Sample size was calculated 51 but we have include at least **55** patients under the study.

Data entry and statistical analysis

The presentation of the Categorical variables was done in the form of number and percentage (%). On the other hand, the quantitative data were presented as the means \pm SD and as median with 25th and 75th percentiles (interquartile range). The data normality was checked by using Kolmogorov-Smirnov test. The cases in which the data was not normal, we used non parametric tests. The following statistical tests were applied for the results: 1. The association of the variables which were quantitative and not normally distributed in nature were analysed using Kruskal Wallis test and variables which were quantitative and normally distributed in nature were analysed using ANOVA. 2. The association of the variables which were qualitative in nature were analysed using Fisher's exact test as at least one cell had an expected value of less than 5. The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 21.0. (trial version), analysis was done on 10 October 2022.

For statistical significance, p value of less than 0.05 was considered statistically significant.

3. Results

A total of 55 patients were enrolled during the defined time period. Comparisons were done between successful outcome and unsuccessful outcome.

Among 55 patients, 20 were female and 35 were male. Among 55 patients, 19 were uneducated and 36 were educated. Among 55 patients, 40 belonged to lower class and 15 belonged to upper class.

On univariate analysis significant factors associated with unsuccessful outcome were: Underweight [BMI] (p-value-0.003), Anemia (p=<.000), Multiple courses in previous (p-value-0.001), previously h/o of ATT (p=0.035), Chest X- ray bilateral (p=0.007), regimen

taken (p-value-0019), late sputum conversion at 3 months (p-value 0.071), at 4 month (p-value 0.001), 9th month (p-value 0.000). On multiple logistic regression analysis factor which were found to be independently and significantly associated with unsuccessful outcome were Anemia (p=0.049).

Table 1: Univariate analysis among patients with successful and unsuccessful outcome.

outcome group						
		Successful		Unsuccessful		P-VALUE
		Count	Column N %	Count	Column N %	
GENDER	Male	16	66.70%	19	61.30%	0.681 Not significant
	Female	8	33.30%	12	38.70%	
EDUCATION	Educated	19	51.35%	18	48.64%	0.21 Not significant
	Uneducated	6	31.57%	13	68.42%	
OCCUPATION	Unemployed	13	43.33%	17	56.66%	0.71 Not significant
	Employed	11	44.00%	14	56.00%	
SOCIAL CLASS	(lower)	1	4.20%	2	6.50%	0.476 Not significant
	Upper	23	43.39%	29	54.71%	
BMI INDEX	<18.5	6	25.00%	22	71.00%	0.003 Significant
	18.5-24.9	17	70.80%	9	29.00%	
	>25	1	4.20%	0	0.00%	

outcome group						
		Successful		Unsuccessful		P-VALUE
		Count	Column N %	Count	Column N %	
H/o Smoking	Yes	9	37.50%	18	58.10%	0.13 Not significant
	No	15	62.50%	13	41.90%	
H/o ATT	Yes	19	79.20%	16	51.60%	0.035 significant
	No	5	20.80%	15	48.40%	
No. of Courses	Single	16	66.70%	8	25.80%	0.01 significant
	Multiple times	3	12.50%	8	25.80%	

H/o 2nd line agents	Yes	1	4.20%	4	12.90%	0.16 Not significant
	No	19	79.20%	17	54.80%	
outcome group						
		Successful		Unsuccessful		P-VALUE
Regimen Taken	Regimen not used	5	20.80%	17	54.80%	0.019 significant
	Recommended and Standard	19	79.20%	13	41.90%	
	Recommended Standard but Modified	0	0.00%	1	3.20%	
outcome group						
		Successful		Unsuccessful		P-VALUE
		Count	Column N %	Count	Column N %	
Contact History	Yes	5	20.80%	10	32.30%	0.34 Not significant
	No	19	79.20%	21	67.70%	
Diabetes	No	45	50.00%	45	50.00%	0.61 Not significant
	yes	4	16.70%	6	19.40%	
Chest X- ray	Unilateral	13	54.20%	6	19.40%	0.007 significant
	Bilateral	11	45.80%	25	80.60%	
Cavity	Yes	12	50.00%	23	74.20%	0.06 Not significant
	No	12	50.00%	8	25.80%	
	Single	8	33.30%	12	38.70%	
	Multiple	2	8.30%	9	29.00%	
Severity of CXR involvement	Minimal	2	8.30%	7	22.60%	0.3 Not significant
	Moderately advance	9	37.50%	12	38.70%	
	Far advance	13	54.20%	12	38.70%	
Anemia	Yes	6	25.00%	24	77.40%	0.000 significant
	No	18	75.00%	7	22.60%	
outcome group						

		Successful		Unsuccessful		P-VALUE
		Count	Column N %	Count	Column N %	
Sputum smear	Scanty Positive ³	0	0.00%	1	3.20%	0.12 Not significant
	1+	14	58.30%	10	32.30%	
	2+	7	29.20%	9	29.00%	
	3+	3	12.50%	11	35.50%	
	M.TB not detected	3	12.50%	2	6.50%	
	M.TB DETECTED	19	79.20%	25	80.60%	
Diagnosis	RIF- Resistant 1	0	0.00%	4	12.90%	0.068 Not significant
	MDR- TB2	24	100.00%	27	87.10%	
Interruptions	Yes	1	4.20%	4	12.90%	0.26 Not significant
	No	23	95.80%	27	87.10%	
3rd Month	NA	1	4.20%	10	32.30%	0.021 significant
	neg	21	87.50%	17	54.80%	
	Positive	2	8.30%	4	12.90%	
4th Month	NA	0	0.00%	23	74.20%	0.000 significant
	neg	23	95.80%	6	19.40%	
	Positive	1	4.20%	2	6.50%	
9th Month	NA	1	4.20%	29	93.50%	0.000 significant
	neg	23	95.80%	2	6.50%	

4. Discussion

One of the major obstacles to the prevention and eradication of TB worldwide is multidrug resistance. In patients receiving full treatment, the cure rate for drug-resistant TB was much lower than the cure rate for drug-sensitive TB. The cost of treating MDR/RR-TB is substantially higher, and many during treatment, people encounter negative medication responses (2)

We carried up research on 55 MDR/RR-TB patients who were given a shorter regimen to learn more about the many factors influencing treatment outcomes. 24 cases were cured, and 8 patients expired, 8 patients were lost to follow-up, and 4 patients had their regimens modified and 11 defaulters.

In our study, significant factors associated with unsuccessful outcome on univariate analysis included underweight [BMI<18.5] (p=0.003), anemia (p=0.001.), sputum of AFB grading, multiple courses (P=0.01), in previous ATT h/o (p=0.35), bilateral chest X-ray (p=0.007), regimen taken (0.019), Anemia (p=0.000) was identified in multiple logistic regression analysis as a factor that was independently and strongly linked with unsuccessful result.

A brief review of different factors which are associated with treatment outcome is as follow: -

BMI

There were 26 underweight patients and 26 normal weight people in our sample of 55 participants, 6 (25%) of the patients who were underweight had a successful outcome, while 22 (71%) did not. Patients with normal weight had a success rate of 17 (70.80%), while 9(29.00%) had an unsuccessful outcome. BMI was statistically related with ($p=0.003$), meaning that patients with normal weight had a higher success rate with the treatment. Patients who were underweight had increased rates of unsuccessful outcomes. Low BMI was found to be a predictor of poor outcome in studies by A. Piubello et al. (3) and Arto Yuwono Soeroto et al. (4) in MDR TB patients who got shorter regimens.

Previous ATT History

20 participants in our sample of 55 patients had no history of ATT, while 35 patients did. 5(20.80%) of the patients with no prior history of ATT had a successful outcome, while 15(48.40%) did not. 19 (79.20%) of the patients with ATT history had successful outcomes, while 16(51.60%) had unsatisfactory outcomes. The outcome of treatment was not substantially correlated with prior ATT history ($P=0.035$). 24 of the 55 patients in our study had only one course of prior ATT, while 11 had several courses from ATT's past. 24 individuals having a history of a single course of ATT had outcomes with 16(66.70%) effective outcomes and 8(25.80%) unsuccessful outcomes. 3 (12.50 %) of the 11 patients with a history of numerous ATT courses had a favorable outcome, while 8 (25.80%) did not. The number of previous ATT courses was found to be statistically substantially correlated with treatment result ($p=0.01$), meaning that patients with a single prior ATT course had higher success rates while patients with several prior courses had less favorable outcomes. The MDR TB patients in Arto Yuwono Soeroto et al (4) study's who got shorter protocol discovered a reduction in history of prior TB treatment ($aRR = 0.80$, 95% CI 0.68 to 0.94) the possibility that a multivariate analysis would be effective.

Anemia

25 Of the 55 participants in our study did not have anemia, while 30 did. Among 18(75%) of the patients who had no anemia had successful outcomes, while 7(22.60%) had unsuccessful. Patients with anemia were treated, 6 (25%) successfully, and 24 (77.40%) unsuccessfully (P -value-0.000). Anemia demonstrated a statistically significant negative correlation with treatment result ($p=0.000$), meaning that patients without anemia had more favorable outcomes than those who did. Patients with anemia had a reduced chance of good outcomes than those without anemia, according to a study by Arto Yuwono Soeroto et al (4).

Chest X ray involvement

36 of the 55 individuals in our study had bilateral CXR involvement, and 19 had unilateral CXR involvement. 6 (19.40%) of the 19 individuals with unilateral CXR involvement had an unsuccessful outcome, while 13(54.20%) had a successful outcome. 36 patients had been Among those who underwent bilateral CXR, 11 (45.80%%) experienced success, while 25 (80.60 %) unsuccessful result. There was statistically substantial chest X-ray involvement connected to treatment results ($p=0.007$) Specifically, patients with unilateral CXR Patients with involvement had better outcomes than those with bilateral CXR involvement had more unsuccessful results. Bilateral illness on a chest x-ray was found to be strongly linked with delayed culture conversion and poor treatment outcomes in investigations of MDR TB patients on prolonged MDR regimens (5,6). Advanced illness at chest radiography was found to be strongly linked with death in a prospective case-control study by R. Singla et al. (7)

Initial Sputum Smear Grading and Sputum conversion

In our study of 55 patients, sputum conversion (at end of 3th month), 38 had sputum smear negative and 6 had had sputum smear positive. Among 38 patients who had sputum smear negative, 21 (87.50%) had successful outcome and 17(54.80%) had unsuccessful outcome. Among 6 patients who had sputum smear positive, 2 (8.30%) had successful outcome and 4 (12.90%) had unsuccessful outcome. Early sputum conversion was statistically significantly associated with successful outcome ($p=0.021$). At end of 4th month 29 had sputum smear negative and 3 had had sputum smear positive. Among 29 patients who had sputum smear negative, 23 (95.80%) had successful outcome and 6(19.40%) had unsuccessful outcome. Among 3 patients who had sputum smear positive, 1 (4.20%) had successful outcome and 2 (6.50%) had unsuccessful outcome. Early sputum conversion was statistically significantly associated with successful outcome ($p=0.000$). The indicator of therapy success in the first two months is sputum conversion. Patients with MDR-TB. (8,9) Monitoring the effectiveness of TB treatment varies depending on short and typical regimens. Results of the TB culture are used to monitor the standard regimen.

TB smear findings are used to monitor a brief regimen. As mentioned by, TB culture data indicate therapeutic efficacy in MDR-TB treatment, and TB culture influences the success of both standard and short-course regimens. (8)

Moreover, mention that the conversion of sputum within the in MDR TB patients, the first two months are a good indicator of treatment success. (8)

Sputum smear conversion is a crucial indicator of how well a treatment will work. (9)

5. Conclusion:

Patients with bilateral chest x-ray involvement, low BMI, ATT history, history of multiple times ATT, high grading sputum positivity, not following recommended and standard regimens, late sputum conversion, and anemia were associated with poor outcome in the current study. Understanding these characteristics may aid in enhancing treatment results, avoiding follow-up delays, and achieving final TB objectives. By resolving these problems, we may also be able to give MDR TB patients on shorter regimens a better prognosis.

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