ORIGINAL ARTICLE

Comparison of the WHO Retreatment Regimen with the Six Drugs Regimen in Patients of Pulmonary Tuberculosis

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[1]Conception, planning of research and writing of the manuscript
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ABSTRACT

Objective: To compare the frequency of early response of WHO retreatment regimen with the six drugs regimen in pulmonary tuberculosis retreatment Category patients.

Study design: Randomized control trial (RCT)

Place and Duration: Chest Department, Fauji Foundation Hospital Rawalpindi from 22nd May 2016 to 22nd November 2016.

Methodology: Patients who had previously been treated for pulmonary tuberculosis for at least 1 month duration and is a failure, relapse or defaulter case presenting in Fauji Foundation Hospital Rawalpindi, both indoor and outdoor were enrolled in the study. Patients were randomized by lottery method to either of the two treatment arms; WHO retreatment regimen or six drug formulations. Clinical features were documented, baseline investigations, AFB smear, Gene Xpert and AFB Culture were sent. Drugs were given on once daily dosage. AFB smear and AFB culture were repeated at 3rd month of treatment. They had a regular follow up in Chest OPD and had monthly visits to the ophthalmology department for visual acuity, fundoscopy and to ENT department for audiometry. Their chest X-ray was done baseline then 3 months. Blood complete picture and liver function tests, serum uric acid, renal function tests were performed baseline, at 2 weeks then 3 months. After their treatment was completed they were followed to look for relapse.

Results: Total 490 patients were included according to the inclusion criteria of the study. Patients were divided into two equal groups. Mean age (years) in the study was 40.00 ± 21.10. There were 33 (6.7) male and 457 (93.3) female patients whereas the frequency of early response of WHO retreatment regimen with the six drugs regimen in pulmonary tuberculosis retreatment category patients was 187 (76.3) and 211 (86.1) respectively which was statistically significant (p-value 0.000).

Conclusion: The study concludes that six drug regimen was superior to WHO standard regimen in the success rate of pulmonary tuberculosis retreatment category patients which useful in bringing new facts regarding management of retreatment category patient in our country as well as worldwide because of the limited research was done on this category of tuberculosis.

Keywords: Tuberculosis, Mycobacterium Tuberculosis, Retreatment regimen

Introduction

Tuberculosis is an infectious disease which is considered to be caused by mycobacterium tuberculosis. It is more common in low – middle socioeconomic status countries and has a fatal outcome if not treated properly. Approximately 9.6 million TB cases were estimated worldwide which is equivalent to 133/100,000 patients including 5.4 million men, 3.2 million women, and 1.0 million children[1].It is also a major public health concern in Pakistan and the estimated the annual incidence of TB in Pakistan is 270/100,000 and prevalence is 341 cases per 100 000 population[1]. The mortality rate of tuberculosis in Pakistan is 26 per 100 000 population[1]. 42,000 new cases per

year are reported and 1.5 million people in our country have tuberculosis[1]. At Global level, tuberculosis is such an infection disease which is considerably be the reason of death due to its myriad presentation and clinical manifestations as well. Similarly, it was estimated that approximately two billion cases were latent tuberculosis at worldwide level in the year 2009 which infact cause mortality of 1.7 people.[2] Furthermore, it was observed that there was decline in the cases of TB in United States whereas the same infectious disease is mostly common in other geographical regions worldwide. Simultaneously, at global level, there is an increasing trend in the percentage of drug-resistance TB with findings states that HIV is considered to be a crucial factor for the emergence and spread of the resistance.[3]

Since 1953, a comprehensive epidemiological data and information about tuberculosis was done under the US centers for Disease Control and Prevention (CDC). In the mid of 80's there was a recovery of tuberculosis was observed. The remarkable increasing trend was mainly observed among minorities of ethnic societies specifically among those who are cases of HIV as well. The fact is that prevention measures in the form of TB awareness programs and campaigns at different levels were intervene in the whole USA and falling trend of TB cases was achieved again.[4]

There was an association of tuberculosis with infection of HIV cases observed vigorously. At worldwide level, this association was more in region of South Africa, following by India and Nigeria. Furthermore, the same study shown that there were twenty to forty times that a person of HIV cases will develop tuberculosis disease.[12]

Globally, this infection disease of tuberculosis is abundant in the region of Africa, following by West Pacific and Eastern Europe. The same regions were endorsed with this infectious disease mainly there are responsible for because of existence of less availability of resources, cases of HIV infectious disease and multidrug-resistant tuberculosis (MDR-TB). In a 2008 report by the WHO, there were new cases of MDR-TB among population of worldwide which was 2.9% in TB whereas there were 15.3% cases of TB which were treated previously following by 5.3% in all new cases of TB. In the region of United States, prevalence of cases of MDR-TB were remarkably elevated with an increasing trend gradually from 0.9% of reported cases of TB in year 2008 to 1.3% of tuberculosis cases in year 2011.[5]

After the emergence of globalization particularly in people living in United States, the standard of living was also improved which in turn is brought radical positive changes for the effective

treatment (streptomycin) in the late 1940s, these number of cases of tuberculosis in the region of United States were an infectious disease of tuberculosis which was gradually declining (126,000 TB patients in 1944; 84,000 in 1953; 22,000 in 1984; 14,000 in 2004), despite explosive growth in the total population (140 million people in 1946, 185 million in 1960, 226 million in 1980). At the national level, since the 1992, there were remarkably increasing trend was seen with respect of recovery of tuberculosis in the United States, the number of TB patients reported annually declined by 61%. In 2011, 10,528 TB patients (a rate of 3.4 cases per 100,000 population) were reported in the United States, representing a 5.8% decreasing trend in the number of reported TB cases and a 6.4% gradually decline in the case rate, compared with 2010.[6] Globally, more than 1 in 3 individuals is infected with TB. According to the WHO, there were 8.8 million incident cases of TB worldwide in 2010, with 1.1 million deaths from TB among HIV-negative persons and an additional 0.35 million deaths from HIV-associated TB. In 2009, almost 10 million children were orphaned as a result of parental deaths caused by TB.[7]

The prevalence of cure in cases of multi-drug resistant tuberculosis ranges from fifty to sixty percentage which was comparable with 95 to 97% for persons with drug-susceptible tuberculosis.[8] It was estimated cure rate for XDR-TB is 30-50%. The cases which are infected with following disease including HIV, MDR-TB and XDR-TB have tendency to produce fulminant and fatal disease; time from exposure of tuberculosis to death averages from two to seven months. Additionally, these cases of tuberculosis form exposure to death are highly infectious, with conversion rates of as much as almost fifty percent in exposed health-care workers. In reaction to these facts and figures, the international organization namely WHO mainly urged and focused its efforts for the development of a plan in order to explore and identify approximately seventy percent of the patients carrying tuberculosis at worldwide level and with the target to completely treat at least eight five percentage of these cases by the end of year 2000. After the intervention of efforts at international level, global detection of smear-positive patients substantially increased ranges from eleven percentage in year 1991 to approximately forty five percentage of smear positive cases of tuberculosis in year 2003, this also include the achievement of target of approximately 71 to 89% of those diagnosed tuberculosis patients to be treated completely.[8]

Case of tuberculosis can be cured by pharmacological therapy efficiently. The regimen which is recommended by World Health Organization (WHO) includes four 1st line drugs i.e. Isoniazid,

Rifampicin, following by Pyrazinamide and Ethambutol for two-month intensive phase then a continuation phase of 4 months treatment with two drugs i.e. Isoniazid and Rifampicin.[2] Despite effective treatment, relapse and failure rate is on rising now. Retreatment is required for those patients who have treatment failure or they default their initial treatment for 2 or more months or if they relapse after initial treatment success. For these patients WHO recommends another regimen which is called retreatment regimen. This regimen is of 8 months duration that includes all five first-line Antituberculous drugs i.e. Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E) and Streptomycin (S) for two months followed by HRZE for 1 month and in continuation phase three drugs HRE for five months.[9]

Limited number of randomized control trials or prospective cohort studies are available on retreatment category patients and this category is a very neglected field of TB treatment. A study conducted on these patients have concluded that this WHO retreatment regimen of five first-line drugs had an overall success rate of 61.4%.[10] Successful outcome in relapse patients was 74.8%, 58.0% in treatment failure and 51.4% in default.[10] Another study on these patients have used 6 drugs and it gives a good outcome of 72%.[11] Although WHO retreatment category guidelines are being followed for years but still it is of great concern that this regimen is leading to poor treatment outcome, increased morbidity and drug resistance.[12] Due to these reasons, some countries have eliminated this WHO retreatment regimen from their national TB control program so there is need of new and effective strategies to treat retreatment category patient's successfully.[12]

For taking an initiative to decline the rate of tuberculosis infectious disease issue by introducing effective therapy in retreatment category patients, we will conduct our study in which we will compare the WHO retreatment regimen that includes 5 drugs with the six drugs regimen in which will include four 1st line antituberculous drugs, an aminoglycoside i.e. amikacin and a fluoroquinolone i.e. levofloxacin for 3 months intensive phase followed by a continuation phase of three drugs HRE for 5 months. We will use levofloxacin as it has a good safety profile and among aminoglycosides, we will use amikacin instead of streptomycin because streptomycin is already a part of WHO retreatment regimen and amikacin have less adverse effects.[13,14]

We will compare the two regimens in their success rate which will be measured by improvement in symptoms, disappearance or regression of cavity, consolidation or opacities on chest x-ray, sputum smear, CT scan and culture conversion from positive to negative. As TB is endemic in our country, its relapse rate is also high and with WHO regimen there is high failure rate so we need a regimen in Pakistan which would treat these patients with a higher success rate without any risk of default or failure.[15] Our study is useful in bringing new facts regarding management of retreatment category patients in our country as well as worldwide because of the limited research done on this category of TB..

Methodology

A Randomized control trial (RCT) was conducted at Chest Department, Fauji Foundation Hospital Rawalpindi. The duration of the study was 22nd May 2016 to 22nd November 2016. Non-probability consecutive sampling technique was used for the purpose of data collection. Total 490 (245 in each group) patients were enrolled in the study with following details of calculation; by using WHO sample size calculator: Confidence level: 95%, Level of significance 5%, Power of test 80%, P_1 WHO regimen: 61.4%[10], P_2 Six drugs regimen: 72%[11]. Patients with age range from 12 -70 years of both gender and history of previous TB treatment (relapse, failure, default) was considered as inclusion criteria. All patients with a history of any of these problems will be excluded from study; Gene Xpert or AFB C/S showing evidence of drug resistance, Extrapulmonary tuberculosis, Hepatic or renal disease, Allergy to any of the medications in the regimen, Pregnancy, Metabolic disease, Immune system disease, Hematological disease, Nervous system and mental disease, Endocrine disease, Malignant disease and patients receiving immunosuppressive therapy.

Early Response considered when Sputum AFB smear and sputum AFB culture become negative by 3th month. Pulmonary TB retreatment Category included Treatment failure: Lack of sputum smear conversion to negative by 5 months of treatment. Default: A patient who has taken at least 1 month of treatment and then it was interrupted for 2 consecutive months or more. Relapse: A patient whose sputum smear becomes negative by 5 months of treatment but reports back after a few months of completion of treatment and sputum smear becomes positive again. WHO Retreatment Regimen included total 8 month's regimen that will include five drugs for initial 2 months; Isoniazid (H)5mg/kg , Rifampicin(R) 10mg/kg, Ethambutol 15 mg/kg (E), Pyrazinamide (Z) 20mg/kg, Streptomycin (S)15mg/kg then for 1 month four drugs HREZ then for 5 months HRE whereas Six Drug Regimen included Total 8 month's regimen that will include for 3 month intensive

phase six drug; Isoniazid(H)5mg/kg, Rifampicin(R)10mg/kg, Ethambutol (E)15mg/kg, Pyrazinamide (Z) 20mg/kg, Amikacin (A)15mg/kg ,Levofloxacin (L)15mg/kg then for 5 months continuation phase three drugs HRE.

Patients who had previously been treated for pulmonary tuberculosis for at least 1-month duration and is a failure, relapse or defaulter case presenting in Fauji Foundation Hospital Rawalpindi, both indoor and outdoor were enrolled in the study. Patients were randomized by lottery method to either of the two treatment arms; WHO retreatment regimen or six drug formulations. Clinical features were documented, baseline investigations, AFB smear, Gene Xpert and AFB Culture were sent. Drugs were given on once daily dosage. AFB smear and AFB culture were repeated at 3rd month of treatment. They had a regular follow up in Chest OPD and had monthly visits to the ophthalmology department for visual acuity, fundoscopy and to ENT department for audiometry. Their chest X-ray was done baseline then 3 monthlies. Blood complete picture and liver function tests, serum uric acid, renal function tests were performed baseline, at 2 weeks then 3 months. After their treatment was completed they were followed to look for relapse. Ethical clearance for the study was obtained from the institutional ethics committee for research.

Patient's data was entered and analyzed by using SPSS software (version 19.0). Descriptive statistics was calculated for qualitative and quantitative variables. For qualitative variables like Gender, retreatment category i.e. defaults or relapse or treatment failure, frequency, and percentages were calculated. For quantitative data like Age, duration of previous no. of patient response treatment, the interval between previous treatment and retreatment. Mean±SD was calculated. Chi square test was used to compare case response between two groups. P-value $\leq$ 0.05 was regarded as significant.

Results

There were 490 cases of tuberculosis were included according to the inclusion criteria of the study. Patients of tuberculosis were randomly divided in two equal groups. WHO retreatment regimen group and six drug formulation group. Mean age (years) in the study was 40.00±21.10 whereas meantime (years) interval between previous treatment and retreatment in the study was 2.95±3.09. There were 33 (6.7) male and 457 (93.3) female patients who were included in the study according as per the inclusion criteria. Frequency of early response of WHO retreatment regimen with the six drugs regimen in pulmonary tuberculosis retreatment category

patients was 440 (59.8) whereas frequency and percentage of reasons for pulmonary tuberculosis retreatment category patients in terms of default, relapse and treatment was 16 (3.3), 455 (92.9) and 19 (3.9) respectively, as shown in Table. No. I

Table I: Descriptive statistics of variables

		Mean+SD
Age (years)		40.00+21.40
Time (years) interval between previous treatment and retreatment		2.95+3.09
		n (%)
Gender	male	33 (6.7)
	female	457 (93.3)
Early Response	yes	440 (89.8)
	no	50 (10.2)
Reasons for Pulmonary Tuberculosis retreatment category	default	16 (3.3)
	relapse	455 (92.9)
	treatment	19 (3.9)

The frequency of early response of WHO retreatment regimen with the six drugs regimen in pulmonary tuberculosis retreatment category patients was 187 (76.3) and 211 (86.1) respectively. Chi-square test was used to compare the frequency of early response of treatment in both the groups which was statistically significant (p-value 0.000), as shown in Table. No. II

Table II: Comparison of Early Response in both the groups

		Two groups		p-value*
		WHO regimen	06 drugs regimen	
Early Response	yes	187 (76.3)	211 (86.1)	0.000
	no	58 (23.8)	34 (13.9)	

*P<0.05 was taken as level of significance

Discussion

One of the most abundant infectious disease considered worldwide is tuberculosis. The disease is mainly caused by *Mycobacterium tuberculosis* MTB.[16] Rifampicin and Isoniazid (INH) alone and combination are mainly two commonly used anti-tuberculosis drugs as MDR-TB is considered to be a crucial problem where bacterium is deemed to be resistant to those two first-line Anti-TB drugs. In year 2012, it was reported that

new cases of tuberculosis infectious diseases was upto 3.7 percentage whereas approximately there 20% of those cases which are already treated previously were prone to have multi resistant drug MDR-TB. The gradual increasing rate of MDR-TB in the region of Eastern Europe and Central Asia, following by few states who have approximately 50% of already treated patients of tuberculosis whereas more than 20% of newly positive cases of tuberculosis infectious disease who have MDR-TB as well. It was estimated that approximately sixty percent of the newly positive diagnosed cases of tuberculosis disease was reported in the region of China, India and Russian Federation.[17] Extensively drug resistant (XDR) TB [isolates as MDR with additional resistance to a fluoroquinolone and any second-line injectable drugs including amikacin, capreomycin and kanamycin. These drug haves been introduced among 92 countries. Furthermore, It was estimated that approximately 9.6% of the MDR-TB cases have tendency to develop XDR-TB.[17]

There were 22 countries who are mostly victimized with the burden of tuberculosis as an infectious disease. These countries includes Pakistan as an under developing country who is at 5th number in bearing the burden of tuberculosis disease and stands at 4th rank number among countries where MDR-TB has become one of the major challenging issue for the practioners to overcome it. In Pakistan, it was reported that near 342 per 100,000 population is likely to have positive tuberculosis which constitutes to the overall percentage of TB patients. It was estimated that percentage of new diagnosed positive cases of tuberculosis with MDR-TB have been increased from 3.5 to 21 percent in the previously treated TB cases. The prevalence of tuberculosis in the country have been increased with many challenging issues and problems which are persist to be the most important reasons including the lack of efforts of effective control programme with regard to tuberculosis, poverty following by illiteracy are adding the main reasons responsible for the increasing percentages of drug-resistant TB among countries.[17]

In our study, mean age (years) in the study was 40.00 ± 21.10. Similarly, the mean age of patients was 45.6 ± 19.75 years.[11] In a study conducted in 2011[11] observed that the frequency and percentage of male cases with positive diagnosed tuberculosis were 62(62) whereas female patients were 38(38). While, in our study, there were 33(6.7) male and 457(93.3) female patients. In our study, WHO retreatment regimen with the six drugs regimen in pulmonary tuberculosis retreatment category patients was 59.8%. Similarly, WHO retreatment regimen of five first-line drugs had an overall success rate of 61.4%.[10] In our study, frequency and percentage of reasons for pulmonary

tuberculosis retreatment category patients in terms of default, relapse, and treatment was 16 (3.3), 455 (92.9) and 19 (3.9) respectively. Similarly, Ottmani et al[3] in their study found that successful outcome in relapse of patients was 74.8%, 58.0% in treatment failure and 51.4% in default.

Conclusion

The study concludes that six drug regimen was superior to WHO standard regimen in success rate of pulmonary tuberculosis retreatment category patients which useful in bringing new facts regarding management of retreatment category patient in our country as well as worldwide because of the limited research was done on this category of tuberculosis.

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