ORIGINAL ARTICLE

Clinical Trial of Linezolid in Treatment of Multi Drug Resistant Tuberculosis at Public sector Hospital Lahore

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ABSTRACT

Background: The new drug for the treatment of multi drug resistant tuberculosis is Linezolid .A few numbers of trials has been conducted globally.
Aim: To determine the clinical effect of Linezolid for management of multi drug resistant tuberculosis patients at Public sector Hospital Lahore.
Methods: Randomized control trial was conducted in outpatient Department of Public sector Hospital Lahore from 1st January 2017 to 30th June 2017 with informed consent from patients of multi drug resistant Tuberculosis of age more than 18 years. The population of whole Punjab was included in this study. Two groups were included. Linezolid group was prescribed Linezolid and Non-Linezolid group without Linezolid in addition to second line of ATT. Each group included 90 patients. The data was analyzed by SPSS version 22.
Results: The mean age of cases in Linezolid group was 32.33± 12.19 years and in non-Linezolid group was 31.87 ± 12.52 years. The median age in both study groups was same i.e. z = -7.16. In linezolid group 51(56.67%) male and 39(43.33%) female and in non-linezolid group 52(57.78%) male and 38(42.22%) were female cases. The gender distribution in both groups was same, In linezolid group 54(60%) cases were cured, 17(18.9%) cases were not cured and 19(21.1%) cases died while in non-linezolid group 30(33.33%) cases cured, 33(36.7%) cases were not cured and 27(30%) cases died. The cure rate was high in linezolid group with low mortality rate.
Conclusion: In randomized control trial with Linezolid, 90% patients of multi drug resistant Tuberculosis were diagnosed with pulmonary Tuberculosis. Treatment with Linezolid drug proved to be effective in 60% cases with no side effect.
Key words; Multi-Drug resistant, randomized control trial, rapid testing, Linezolid

INTRODUCTION

Tuberculosis was declared a "global health emergency" in 1993 by World Health Organization.[1] and the Global plan was developed in 2006 to stop Tuberculosis by stop TB partnership and there is aim for saving 14 million lives till the end of 2015.[2-5]According to 2012, the recommended management of new cases of pulmonary tuberculosis, is six months with a combination of antibiotics containing isoniazid,, rifampicin pyrazinamide, and ethambutol for the period of first two months, and only isoniazid and rifampicin for the rest four months[1,6]. If resistance develops to isoniazid, ethambutol can be added for the period of last four months as an alternative[2,7-9]. The treatment with second-line drugs for Multi-Drug Resistant Tuberculosis includes usually minimum four or more anti-TB drugs for a minimum period of 6 months, and possibly for maximum period of 18–24 months if rifampin resistance has been developed and identified in the specific strain of Tuberculosis. Second-line drugs have fewer efficacies with more toxicity and these are much more expensive than first-line drugs. Multi-Drug Resistant Tuberculosis cure rates can approach 70% under ideal program conditions[3,10].

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A number of set targets will be achieved by the end of 2015, mostly the emerging cases of multiple drug-resistant tuberculosis and the increase in tuberculosis associated with HIV.[6,11] A system of classification of Tuberculosis is used primarily in public health programs which is developed by the American Thoracic Society[7,12-14].

In Pakistan no trial has been conducted so for to determine the efficacy and side effects of Linezolid. So it is intended to conduct clinical trial of Linezolid in Pakistan especially in Punjab where patients of multi drug resistance in Tuberculosis are visiting outpatient department of public sector Hospital from all over the country. The purpose of clinical trial is to find out efficacy and side effects of Linezolid among multi drug resistance Tuberculosis patients in Pakistan.

METHODOLOGY

Randomized control trial was conducted in outpatient department of a Public sector Hospital, Lahore from 1st January 2017 to 30th June 2017 after taking informed consent from patients of multi drug resistant Tuberculosis (of age more than 18 years). After convenient sampling, the population comprised of patients coming from whole Punjab was included in this study. Group 1 those took Linezolid and group 2 did not take Linezolid in addition to second line ATT. Each group included 90 patients. Data

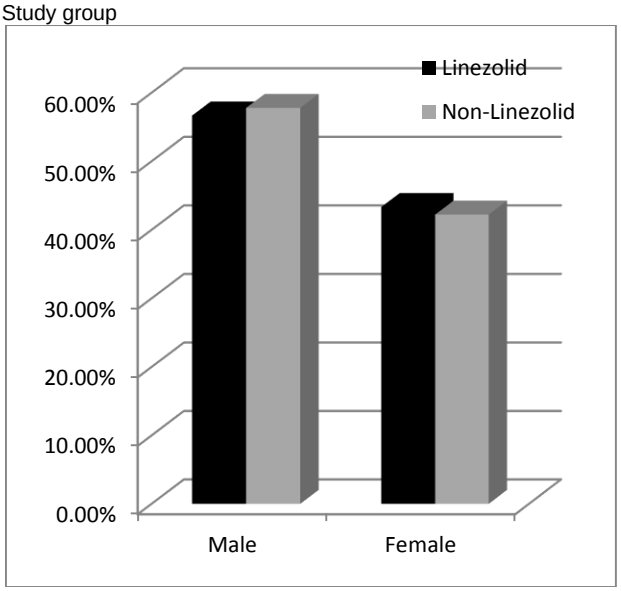
were collected on a specified questionnaire by a doctor and his team and required information regarding the disease was collected after interviewing the patients. The data were entered and interpreted as frequency and percentage distribution. Only registered patients of multi drug resistant Tuberculosis those fulfilling the inclusion criteria were included in this study. The data were analyzed by SPSS version 22.

RESULTS

The mean age of cases in Linezolid group (Group 1) was 32.33 ± 12.19 years and in non-Linezolid group (Group 2) was 31.87 ± 12.52 years. The median age in both study groups was same i.e. z = -7.16 and p-value = 0.074.

	Linezolid	Non linezolid	Total
Mean	32.33	31.87	32.10
SD	12.19	12.52	12.32
Median	29.5	28	29
IQR	12.5	17.50	15
Minimum	15	18	15
Maximum	68	74	74

Majority of the cases in both groups belonged to 18-44 years age group. In Linezolid group there were 51(56.67%) males and 39(43.33%) females and in non-linezolid group, 52(57.78%) males and 38(42.22%) females. The gender distribution in both study groups was same, p-value > 0.05. Chi-square test = 0.023.



In this study 88(97.80%) cases from group-1 and 89(98.90%) cases from group-2 were suffering from pulmonary cases whereas 02(2.20%) cases from group-1 and 01(1.10%) cases were suffering from extra pulmonary.

Site of DR-TB	Study groups		Total
	Linezolid	Non-linezolid	
Pulmonary	88(97.8%)	89(98.9%)	177(98.3%)
Extra pulmonary	2(2.2%)	1(1.1%)	3(1.7%)
Total	90(100%)	90(100%)	180(100%)

In group 1 34(37.80%). 56(62.20%) cases from group 1 and 42(46.70%) cases from group-2 belonged to Lahore whereas 56(62.20%) cases from group 1 and 48(53.30%) cases in group 2 belonged to other cities of Punjab. In this study 30(33.30%) cases from group 1 and 34(37.80%) cases from group 2 were house wives, 11(12.20%) cases from group 1 and 13(14.40%) cases from group 2 were students. Whereas 45(50.00%) patients from group 1 and 42(46.70%) patients from group 2 were self-employed. 04 (4.40%) cases from group 1 and 01(1.10%) case from group 2 belonged to other professionals.

Occupation	Study groups		Total
	Linezolid	Non-linezolid	
House wife	30(33.3%)	34(37.8%)	64(35.6%)
Students	11(12.2%)	13(14.4%)	24(13.3%)
Own work	45(50%)	42(46.7%)	87(48.3%)
Others	4(50%)	1(1.1%)	5(2.8%)
Total	90(100%)	90(100%)	180(100%)

In this study 14(14.40%) cases from group 1 and 13(13.30%) cases from group 2 completed their previous treatment for Tuberculosis, 13 (14.40%) cases from group 1 and 15(16.70%) cases from group 2 had treatment failure, 06 (6.70%) cases from group 1 and 04(4.40%) cases group 2 were lost. Treatment could not be evaluated among 58(64.40%) cases from group 1 and 59(65.60%) cases from group 2.

Previous Tuberculosis (Episodes-outcome)	Study groups		Total
	Linezolid	Non-linezolid	
Completed	13(14.4%)	12(13.3%)	25(13.9%)
Failed	13(14.4%)	15(16.7%)	28(15.6%)
Lost to follow up	6(6.7%)	4(4.4%)	10(5.6%)
Treatment not evaluated	58(64.5%)	50(65.6%)	117(65%)
Total	90(100%)	90(100%)	180(100%)

Treatment outcome	Study groups		Total
	Linezolid	Non-linezolid	
Cured	54(60%)	30(33.3%)	84(46.7%)
Failed	17(18.9%)	33(36.7%)	50(27.8%)
Died	19(21.1%)	27(30%)	46(25.6%)
Total	90(100%)	90(100%)	180(100%)

Only 04(4.40%) cases from group 1 and 10(11.10%) cases from group 2 were smokers. 86(95.60%) cases from group 1 and 80(88.90%) cases from group 2 were nonsmokers. Diagnostic culture was positive in 58(64.40%) cases from group 1 and 70(77.80%) cases from group 2.Though it was negative among 32(35.60%) cases from group 1 and 20(22.20%) cases from group 2 but it did not mean that these patients were not having resistance to Rifampicin .There might be low number of bacteria, low concentration or weak media. For confirmation of resistance rapid testing (Gene-X pert) was done that gave positive results in both groups. p- value = 0.048. In Linezolid group 54(60%) cases cured, in 17(18.9%) cases treatment was failed, 19(21.1%) cases died due to other causes while in non-Linezolid group 30(33.33%) cases cured, in 33(36.7%) cases treatment was failed and 27(30%) cases died. The cure

rate was high in Linezolid group with lower mortality rate, p-value = 0.001.

DISCUSSION

In randomized control trial with Linezolid, two groups were taken, group-1 that is also called Linezolid group and group-2 which is called Non-Linezolid group. Each group had 90 cases of multi-drug resistant Tuberculosis. Both groups were given second line of anti-tuberculosis drugs but group-1 was also given Linezolid in addition. The mean age of cases in Linezolid group was 32.33 ± 12.19 years and in non-Linezolid group was 31.87 ± 12.52 years. The median age in both study groups was same i.e. z = -7.16 and p-value = 0.0747.

In clinical trial majority of the cases belonged to age group 18-34 years. In linezolid group there were 56.67% male and 43.33% female cases and in non-linezolid group there were 57.78% male and 42.22% female cases. The gender distribution in both study groups was same with p-value > 0.05 and Chi-square test = 0.023. Approximately 40% from both groups were residents of Lahore whereas rests of the cases were from other cities. Other cities included Gujranwala, Gujarat, Sheikhupura and Sialkot etc. 33.37% female participants were housewives whereas only 12% were students and others were having own work, It was meant those were having their own businesses and not so careful about their health. History of contact might be positive in this category. Previous treatment was evaluated in majority of the cases of multi-drug resistant Tuberculosis. A few cases were smokers in this study. More than 98.00 % patients were suffering from pulmonary Tuberculosis. Sputum culture was positive in 54.77% cases of both groups before starting treatment.

In the treatment of MDR-TB and XDR-TB, the efficacy had been shown by a drug Linezolid. This had been proved in 5 case series. Despite this drug have many side and toxic effects. This had been proved by many studies. These included suppression of bone marrow, optic and peripheral neuropathy, leading to minimum use of this drug. Park et al found conversion of positive culture to negative in eight HIV- patients but proved maximum side effects with a daily dosage of 600mg mg of linezolid; there was development of peripheral neuropathy in four patients, development of optic neuropathy in two patients, and development anemia in one patient. There was death of two patients so there was discontinuation of management with this drug. This had been concluded that linezolid is effective with poor toleration. There was report of ten multi drug resistant Tuberculosis patients by von der Lippe et al. There was development of side effects lead to discontinuation the drug in seven patients. Successful treatment with this drug was among five patients with by Fortun et al. In a study by Migliori et al 85 patients of multi drug resistant Tuberculosis and extensively drug resistant Tuberculosis at Germany who had treatment with the drug linezolid, 32% discontinued treatment due to side effects. It is pertinent to mention those who discontinued drug were taking 600-mg B.D in a day[8,15, 19].

In this study Previous Tuberculosis (Episodes-outcome) treatment was completed in 14.40% cases in Linezolid group and 13.30% cases in non-Linezolid group. There was failure in 14.40% cases in Linezolid group and 16.70% in non-Linezolid group. Previous treatment could not be evaluated in 64.40% cases in Linezolid group and 65.50% cases in non-Linezolid group.6.70% cases from Linezolid group and 4.40% cases from non-Linezolid group were not available for follow up. Smoking was associated with 4.40% cases in Linezolid group and 11.10% cases in non-Linezolid group with p-value 0.059 and chi-square test 2.98. 97.80% cases from Linezolid group and 98.90% cases from non-Linezolid group were pulmonary Tuberculosis whereas extra. Pulmonary Tuberculosis was present in 2.20% cases in Linezolid group and 1.10% cases in non-Linezolid group.

In diagnostic culture 64.4% cases in Linezolid group and 77.80% was shown in non-Linezolid group showed positive culture whereas 35.60% cases in Linezolid group and 22.20% cases from non-Linezolid showed negative culture. Negative culture reports didn't mean that patients were not resistant to ATT because negative result might be due start of treatment just after result of rapid diagnostic test. If initially culture test is negative that will become positive without improvement. For verification of diagnosis and to start early treatment, rapid diagnostic test includes Gene X-pert test was done. The purpose of that test was to detect Mycobacterium Tuberculosis, to confirm resistance against Rifampicin and to start earliest possible treatment. This is very important that result of rapid diagnostic test was received after two hours whereas results of diagnostic culture is available after 6 to 8 weeks. All cases in both groups showed resistance to RIFAMPICIN. In rapid diagnostic test earliest possible results were there and treatment was started. Both groups were given second line of ATT but group 1 was given Linezolid in addition. The cases were followed by culture and blood test. After negative results for consecutive three times, it was labeled that recovery is proceeding. The cure rate in Linezolid group was 60.00% and in non-Linezolid group was 33.30%.There was failure of treatment in 18.90% cases in Linezolid group and 36.70% cases in non-Linezolid group. 21.10% patients died in Linezolid group and 30.00% in non-Linezolid group. The death of the patients was due to other causes. No serious side effects were noted. Minor side effects like vomiting, pain abdomen, heart burn and diarrhea were observed in few cases but these side effects could be due to any drug used for the treatment of Tuberculosis. Linezolid is effective drug and can be used safely in treatment of multi-drug resistant Tuberculosis with the dosage of 600 mg twice a day for 36 weeks.

CONCLUSION

In randomized control trial with Linezolid, 90% cases multi drug resistant Tuberculosis were pulmonary Tuberculosis. 100% cases in both groups were resistant to RIFAMPICIN. Treatment with Linezolid proved to be effective in 60% cases with no side effect in. It was proved Linezolid drug is effective in treatment of multi drug resistant Tuberculosis with the combination of other second line drugs for the management of Tuberculosis.

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