ORIGINAL ARTICLE

Addition of Amikacin and Levofloxacin is Associated with Higher Culture Conversion Rate in Pulmonary Tuberculosis

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ABSTRACT

Objective: To study that addition of Amikacin and Levofloxacin to the standard anti-tuberculosis regimen is associated with higher culture conversion rate at 02 months.
Study Design: Randomized controlled trial
Place and Duration of Study: Department of Medicine CMH Lahore Medical College January 2009 to December 2010.
Materials and Methods: Hundred patients with sputum culture positive tuberculosis were selected by non probability convenient sampling. Patients were divided into two groups by randomization. Group1 received HREZ (INH, Rifampicin, and Ethambutol and PZA) and Group2 received two additional drugs i.e. Levofloxacin per oral daily and injection Amikacin IV daily. Sputum culture was repeated at the end of 02 months of treatment and percentage of culture conversion in each group was determined. Data was collected through a carefully designed structured data collection form and analyzed by SPSS version 18. Frequencies and percentages of different variables were calculated. Comparison of means was done by student t test and frequencies and percentages were compared by chi square test and fisher exact test. P value <0.05 was considered significant.
Results: Mean age was 48.46±17.76 and 50.82±17.59 (P=0.506) in Group1and Group2, respectively. Group1 included 31(62%) male and 19(38%) female while Group2 included 40(80%) male and 10(20%) female (P= 0.077). In group 1 (on standard ATT) 42(84%) were culture negative and in group 2(standard ATT plus Levofloxacin and Amikacin) 49(98%) were culture negative at two months (P=0.0309)).
Conclusion: Addition of Amikacin and Levofloxacin to standard ATT regimen is associated with higher culture conversion rate at 02 months. The regimen containing Amikacin and Levofloxacin was not associated with any adverse reactions and tolerated well by the patients.
Key words: Pulmonary Tuberculosis, culture conversion, Amikacin, levofloxacin.

INTRODUCTION

Tuberculosis (TB) remains the burden on the health care resources despite the early case detection, directly observed treatment strategies, improved cure rates and effective control measures. In 2009, 5.8 million cases of TB (new cases and relapse cases) were notified to national tuberculosis control programme (NTP) or equivalent NTPs. Among pulmonary cases, 57% of global notifications were sputum smear-positive. Among the 22 high burden countries, the percentage of notified cases of pulmonary TB that were sputum smear-positive was relatively low in Zimbabwe (29%), the Russian Federation (31%), Pakistan (42%),Myanmar (45%), Kenya (46%) and Ethiopia (46%). A comparatively high proportion of notified cases were sputum smear-positive in Bangladesh (81%), the Democratic Republic of the Congo (85%) and Viet Nam (73%). The treatment outcome rate for new smear positive cases varies in different countries 57% (Russian federation) to 95% (Cambodia).In Pakistan the success rate for new smear positive cases is 90%[1].

As a general principle rate of clearance of Mycobacterium tuberculosis may serve as a surrogate marker for the adequacy of its eradication. The best studied surrogate marker for cure of tuberculosis is sputum culture conversion after 2 months of chemotherapy. It is a sensitive biomarker of adequacy of treatment. It can predict long term cure and relapse[2].

Despite the high cure rate achieved and claimed word wide by tuberculosis control programme the culture conversion rate at two months varies from 51% to 95% as observed in various studies. The Mean time to culture conversion is 4.8 ± 3.7[3,4,5]. With increasing incidence of Multidrug Resistant (MDR) and Extensively Drug Resistant (XDR) TB it is quite obvious that that in future studies the expected culture conversion rate would be much lower[6,7,8].

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The variables associated with lack of sputum smear or culture conversion are age >45 yr, higher pre-treatment smear and culture grading, extent of the radiographic involvement (cavitation and bilateral lung involvement) non DOT managed and DM[9,10,11]. It is not possible to predict exactly the time to obtain negative sputum smears and cultures after an initiation of treatment[12].

Although smear negative patients are less infectious the only absolute marker of infectivity is culture conversion. Patients with smear-negative, culture-positive TB are still able to transmit disease to others[13]. A culture negative patient is unlikely to transmit the infection. Sputum smear and culture positive patients with pulmonary TB are the major source for the spread of TB. Prevention of transmission of mycobacterium is back bone of control and prevention of tuberculosis and this can also significantly reduce the number of new cases. Sputum culture conversion, therefore, is also an important indicator for the infectivity of a patient with pulmonary TB and is land mark achievement in the prevention and control of tuberculosis[3,14].

According to the guidelines issued by American Thoracic Society, Centers for Disease Control and Prevention (CDC), and the Infectious Diseases Society of America patients suspected of having or known to have tuberculosis should be kept in isolation rooms. This recommendation should also be also apply to patients returning to households that have infants or immunocompromised individuals. However, compliance with respiratory isolation is not adequately practiced in multiple centers in the United States and Europe[15,16]. In developing countries like Pakistan it is not possible to arrange the respiratory isolation for all smear positive patients due to limited resources. Bacteriological monitoring is not routinely done after initiation of therapy due non availability or lack of facility. With above mentioned circumstances it is of paramount importance that the period of infectivity tuberculosis patients is minimal. We must develop and promote the he regimen with higher early bactericidal activity to render the patient non infectious for health care workers, close contacts and general population. Anti tuberculosis regimens with superior sterilizing activity at 2 months have lower relapse rates, and this parameter can be used as an early indicator of the relative efficacy of various regimens[17,18].

Amikacin and Ciprofloxacin are very effective 2nd line anti-tuberculosis drugs against M tuberculosis isolates. In vitro studies show that, M. tuberculosis isolates, 98% were sensitive to Amikacin and 97% to Ciprofloxacin[19]. Various studies using flouroquinolones as antituberculosis drug has shown promising results. In 2010 Wang J-Y et al demonstrated a culture conversion rate of 82% with use of moxifloxacin as an additional drug and the culture conversion rate was 61% with standard ATT in the same study[3]. The efficacy of Amikacin along with one of the quinolones as an addition to standard ATT regimen has not been studied earlier. In this study we tested the hypothesis that addition of levofloxacin and Amikacin to standard ATT is associated with higher rate of sputum culture conversion after 02 months of therapy.

AIM

To study that addition of Amikacin and levofloxacin to the standard anti-tuberculosis regimen is associated with higher culture conversion rate at 02 months.

MATERIALS AND METHODS

It was a randomized controlled trial undertaken in the Department of Medicine Combined Military Hospital Lahore from January 2009 to December 2010. Approval of the Institutional ethical review committee was obtained. Both indoor and outdoor patients of more than 12 years of age were included in the study. After detailed history and thorough physical examination a total of 100 patients with sputum culture positive tuberculosis were enrolled by non probability convenient sampling. Patients with previous history of TB, drug resistant cases on baseline AFB culture, extra-pulmonary TB, HIV positive patients and known intolerance or allergy to any of the drugs studied. Patients with renal failure, impaired liver functions, epilepsy and uncontrolled diabetes mellitus were excluded from the study. Written consent was taken. Patients were divided into two groups by randomization. Group1 received HREZ (INH, Rifampicin, and Ethambutol and PZA) and Group 2 received two additional drugs i.e. Levofloxacin per oral daily and injection Amikacin IV daily. All drugs were administered as per kg body weight. Baseline drug sensitivity testing was obtained by using BACTEC to get results within 30 days. Sputum culture was repeated at the end of 02 months of treatment. Blood complete picture, X- ray chest, serum urea, Serum creatinine, serum uric acid, liver function tests and urine routine examination was done at baseline. Renal function test, liver function tests and blood complete picture were done every two weeks. Patients who developed symptoms of adverse drug effects were monitored more frequently.

Data was collected through a carefully designed structured data collection form and analyzed by SPSS version 18. Frequencies and percentages of different variables were calculated. Comparison of means was done by student t test and frequencies

and percentages were compared by chi square test and fisher exact test.

RESULTS

A total of 100 patients were included in the study and divided into two groups of equal size by randomization. The descriptive statistics of both groups are shown in the Table.1The baseline descriptive characteristics are similar in both group 1 and 2. In group 1 (on standard ATT) 42(84%) were culture negative and in group 2 (standard ATT plus Levofloxacin and Amikacin) 49(98%) were culture negative at two months (P= 0.0309). The frequencies of adverse drug reaction observed in both groups are shown in the Table.2.There was no significant difference in incidence of adverse drug effects between group 1 and group2 .No treatment modification was done due to adverse drug effects and there was not a single drop out in both groups.

Table: 1 Descriptive Characteristics of Patients

Variable	Group 1	Group2	P value
Mean Age	48.46±17.76	50.82±17.59	0.50
Minimum Age (Years)	16	18	-
Maximum Age (Years)	89	88	-
Male	31(62%)	40(80%)	.077
Female	19(38%)	10(20%)	.077
Smoker	10(20%)	12(24%)	0.60
Bilateral Lung disease	11(22%)	12(24%)	1.00
Anemia Hb <11gm/L	7(14%)	8(16%)	0.84

Table 2 Frequency of Adverse Events

Variable	Group 1	Group 2	P value	Odds ratio	95% Confidence interval
Vertigo	8 (16%)	9(18%)	0.85	0.86	0.41 to 1.81
Tinnitus	7(14%)	8(16%)	0.84	0.85	0.39 to 1.86
Blurred Vision	6(12%)	5(10%)	0.82	1.22	0.50 to 2.98
Headache	4(8%)	7(14%)	0.25	0.53	0.21 to 1.33
Insomnia	5(10%)	8(16%)	0.29	0.58	0.25 to 1.35
Allergic Reaction	6(12%)	5(10%)	0.82	1.22	0.50 to 2.98
Nausea and Vomiting	8(16%)	9(18%)	0.85	0.86	0.41 to 1.81
Creatinine >120µmol/L	5(10%)	7(14%)	0.51	0.68	0.28 to 1.61
Serum ALT > 100 U/L	10(20%)	12(24%)	0.60	0.79	0.40 to 1.54
Hyperuricemia*	11(22%)	12(24%)	1.00	1.01	0.52 to 1.94
Thrombocytopenia†	6(12%)	5(10%)	0.82	1.22	0.50 to 2.98

*Hyperuricemia : Male > 0.33 µmol/L Female > 0.18–0.41 µmol/L †Platelet < 100 ×109/L)

DISCUSSION

Our study revealed that addition of Amikacin and levofloxacin to standard ATT regimen in the intensive phase is associated with higher culture conversion rate. The culture conversion rate at 02 months is the validated surrogate marker of bactericidal activity of a regimen and it can predict the long term cure rate and incidence of relapse. The higher two months culture conversion is associated with higher cure rate and non infectivity of the patients. This fact was first demonstrated by Mitchison in 1993 and late on confirmed by Yew WW et al and Benator D et al in 2000 and 2002, respectively. The 2-month culture conversion is the best current surrogate marker predictive of good long-term treatment outcome[20,21,22].

The findings of our study are consistent with other study by J-Y. Wang in 2010 The addition of moxifloxacin to standard ATT was associated with a higher culture conversion at 06 weeks but the study failed to show any increase in culture conversion rate at 02 months[3]. Our study has reported a significant increase in culture conversion at 02 months and it means the 06 drug regimen is superior in achieving a better long term cure.

Different studies have shown that addition of a bactericidal aminoglycoside (streptomycin) to Isoniazid, Rifampicin and PZA is associated with a higher sputum culture conversion at 02 months[23]. Prevalence of MDR and XDR TB is rising worldwide and in Pakistan as well .The primary drug resistance to streptomycin is 5.4% to 19% as reported in various studies. Our study has revived an already proven fact that the aminoglycosides containing regimen is associated with higher culture conversion rate. We

demonstrated this fact with a relatively new aminoglycoside but the results are comparable to previous studies done with regimens containing streptomycin[24,25,26].

An important implication of our study is that by using this 06 drug regimen we are confident enough that our patients are noninfectious at most after 02 months and they are no more a potential source of tuberculosis to general public, close contacts and health care workers. This regimen can be recommended to be followed in patients who have risk factors known to be associated with delayed culture conversion. This fact is of prime importance in the countries where bacteriological monitoring is not available or is not done routinely to reduce the cost of treatment and also where the facilities for respiratory isolation are very limited.

The limitations of our study is a smaller sample size ,failure to calculate the average time from treatment to culture conversion, lack of analysis of risk factors for delayed culture conversion and no follow up the patients beyond two months. So we are unable to validate the long term effects of higher culture conversion rate observed in our study. We recommend that further study with a larger sample size, with calculation of average time from treatment to culture conversion as well as analysis of risk factors causing delayed culture conversion should be planned so that the definite recommendation for 06 drug regimen can be formulated. We also recommend a study with long term follow up of the patients so that the effect of culture conversion at 02 months on relapse rate and long term cure can validated.

CONCLUSION

Addition of Amikacin and Levofloxacin to standard ATT regimen is associated with higher culture conversion rate at 02 months. The regimen containing Amikacin and Levofloxacin was not associated with any adverse reactions and tolerated well by the patients. This regimen can be recommended to be followed in patients who have risk factors known to be associated with delayed culture conversion.

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