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ADDITION OF LEVOFLOXACIN AND AMIKACIN IS RELATED WITH ADVANCED CULTURE CONVERSION RATE IN PULMONARY TUBERCULOSIS

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Abstract:

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.*

Study design: *Randomized controlled trial*

Place and duration of studies: *In the Medicine Unit-II of Bahawal Victoria Hospital, Bahawalpur for one-year duration from May 2019 to May 2020.*

Materials and methods: *One hundred tuberculosis patients with a positive sputum culture result were selected by a method unusual for the probability of sampling. The patients were divided into two groups using the randomization method. Group 1 received HREZ (INH, rifampicin and ethambutol and PZA) and group 2 received two additional medications ie levofloxacin orally daily and Amikacin IV injection daily. The sputum culture was repeated at the end of the 02-month treatment, and the percent culture conversion in each group was determined. Data was collected using a carefully designed, structured data collection template and analyzed using SPSS version 18. The frequencies and percentages of various variables were calculated. The comparison of the means was made using the Student's t-test and the frequencies and percentages were compared using the chi-square test and the Fisher's exact test. A p value of <0.05 was considered significant.*

Results: *The mean age was 48.46 ± 17.76 and 50.82 ± 17.59 (p = 0.506) in Groups 1 and 2, respectively. Group 1 consisted of 31 (62%) men and 19 (38%) women, while when Group 2 included 40 (80%) men and 10 (20%) women (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: *The addition of amikacin and levofloxacin to the standard ATT regimen is associated with a higher culture conversion rate after 2 months. The regimen containing amikacin and levofloxacin was not associated with any side effects and was well tolerated by patients.*

Key words: *pulmonary tuberculosis, culture conversion, amikacin, levofloxacin.*

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INTRODUCTION:

Tuberculosis (TB) remains a burden on healthcare resources despite early case detection, direct follow-up treatment strategies, better cure rates and effective control measures. In 2009, 5.8 million cases of tuberculosis (new cases and relapses) were reported to the National Tuberculosis Control Program (NTP) or equivalent NTPs. Among lung cases, 57% of global reports were positive for sputum smear. Among the 22 countries with high stress, the proportion of reported pulmonary tuberculosis cases with sputum smear detected was relatively low in Zimbabwe (29%), the Russian Federation (31%), Pakistan (42%) and Myanmar (45%). , Kenya (46%) and Ethiopia (46%). Sputum smears were positive in Bangladesh, Democratic Republic of Congo (85%) and Vietnam (73%), Bangladesh (81%), Democratic Republic of Congo (85%) and Vietnam (73%). The treatment outcome rate for new cases of positive swabs varies across countries from 57% (Russian Federation) to 95% (Cambodia). In Pakistan, the success rate of new smear cases is 90%.

As a general rule, the rate of Mycobacterium tuberculosis clearance may serve as a surrogate marker for correct control. The best-studied surrogate marker of tuberculosis cure is conversion of sputum culture after 2 months of chemotherapy. It is a sensitive biomarker of treatment adequacy. It can predict long-term recovery and relapse.

Despite the high cure rate achieved and reported worldwide by the TB control program, the conversion rate of cultures after two months ranges from 51% to 95% as observed in various studies. The mean time to culture conversion is 4.8 ± 3.7. As the incidence of multi-drug resistant tuberculosis (MDR) and extensively drug resistant tuberculosis (XDR) increases, it is quite clear that in future studies the expected conversion rate of cultures will be much lower.

Variables associated with the absence of a sputum smear or culture conversion are age> 45 years, higher score of smear and culture before treatment, the extent of radiographic changes (cavitation and bilateral lung involvement) without DOT and DM treatment. It is not possible to accurately predict when the negative smears and sputum cultures will be obtained after initiation of treatment.

Although patients with a negative smear are less infectious, the only absolute indicator of infectivity is culture conversion. Patients with non-smearing tuberculosis who are culture positive may still transmit the disease to others. It is unlikely that a culture negative patient will transmit an infection. Sputum smear and culture-positive patients with pulmonary tuberculosis are the main source of the spread of tuberculosis. Prevention of the transmission of mycobacteria is fundamental to the control and prevention of tuberculosis, and can also significantly reduce the number of new cases. Therefore, the conversion of sputum cultures is also an important indicator of the infectivity of a patient with pulmonary tuberculosis, and is a significant achievement in the prevention and control of tuberculosis.

According to guidelines issued by the American Thoracic Society, Centers for Disease Control and Prevention (CDC), and the Infectious Diseases Society of America, patients suspected of having tuberculosis or known to have tuberculosis should be kept in solitary confinement. This recommendation should also apply to patients returning to households with infants or immunocompromised people. However, airway isolation is not properly practiced in many centers in the United States and Europe. In developing countries such as Pakistan, it is not possible to provide airway isolation for all smear positive patients due to limited resources. Bacteriological monitoring is not routinely performed after initiation of therapy due to non-availability or non-availability of a facility. Under these circumstances, it is extremely important that the duration of tuberculosis infection is kept to a minimum. We must develop and promote a regimen with a higher early germicidal effect to make the patient non-infectious to healthcare professionals, close contacts and the general population. Anti-tuberculosis regimens with better sterilizing activity after 2 months have lower rates of relapse and this parameter can be used as an early indicator of the relative effectiveness of different regimens.

Amikacin and Ciprofloxacin are very effective second-line anti-tuberculosis drugs against M. tuberculosis isolates. In vitro studies show that 98% of M. tuberculosis isolates were sensitive to amikacin and 97% to ciprofloxacin. Various studies using fluoroquinolones as an anti-tuberculosis drug have produced promising results. In 2010, Wang J-Y et al. In the same study demonstrated a culture conversion rate of 82% using moxifloxacin as an additional drug, and the culture conversion rate was 61% with standard ATT. The effectiveness of Amikacin together with one of the quinolones as an addition to the standard ATT regimen has not been studied before. In this study, we tested the hypothesis that the addition of levofloxacin and amikacin to standard ATT was associated with a

higher sputum culture conversion rate after 2 months of treatment.

MATERIALS AND METHODS:

It was a randomized controlled trial conducted at the Medicine Unit-II of Bahawal Victoria Hospital, Bahawalpur for one-year duration from May 2019 to May 2020. Ethics Review Committee approval was obtained. The study included patients over 12 years of age, both indoors and outdoors. After a detailed interview and careful physical examination, a total of 100 tuberculosis patients with positive sputum culture were enrolled in the study by atypical sampling. Patients with a history of tuberculosis, drug-resistant cases in the initial culture of AFB, extrapulmonary tuberculosis, HIV-infected patients and known intolerance or allergy to any of the drugs tested. Patients with renal failure, hepatic impairment, epilepsy and uncontrolled diabetes were excluded from the study. Written consent has been taken. The patients were divided into two groups using the randomization method. Group 1 received HREZ (INH, rifampicin and ethambutol and PZA) and group 2 received two additional drugs, ie levofloxacin daily orally and daily intravenous amikacin injection. All drugs were administered per kg body weight. Baseline drug susceptibility testing was obtained using BACTEC to obtain results within 30 days. Sputum culture was repeated at the end of 2 months of treatment. A complete blood count, chest X-ray, serum urea, serum creatinine, serum uric acid, liver function tests and routine urinalysis were performed at the start of the study. Kidney function tests, liver function tests and complete blood counts were performed every two weeks. Patients who experienced symptoms of adverse drug reactions were monitored more frequently.

Data was collected using a carefully designed, structured data collection template and analyzed using SPSS version 18. The frequencies and percentages of various variables were calculated. The comparison of the means was made using the Student's t-test and the frequencies and percentages were compared using the chi-square test and the Fisher's exact test.

RESULTS:

A total of 100 patients were enrolled in the study and randomized into two groups of equal size. The descriptive statistics of both groups are presented in Table 1. The baseline descriptive features are similar in both groups 1 and 2. In group 1 (with 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 reactions observed in both groups are presented in Table 2. There was no significant difference in the incidence of adverse drug reactions between Group 1 and Group 2. There was no treatment modification due to adverse drug reactions and there was no single accident 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

DISCUSSION:

Our study showed that the addition of amikacin and levofloxacin to the standard intensive phase ATT regimen was associated with a higher culture conversion rate. The culture conversion rate at 02 months is an approved surrogate marker for regimen bactericidal activity and can predict the long-term cure rate and relapse rate. A longer culture conversion after two months is associated with a higher cure rate and no patients are infectious. This fact was first demonstrated by Mitchison in 1993 and later confirmed by Yew WW et al. And Benator D et al. In 2000 and 2002, respectively, 2-month culture conversion is now the best surrogate marker for predicting good long-term results. treatment results.

Our study results are in line with other J-Y studies. Wang in 2010. The addition of moxifloxacin to the standard ATT was associated with a higher conversion of the culture after 6 weeks, but the study showed no increase in the conversion rate of the culture after 2 months3. Our study showed a significant increase in culture conversion after 02 months, meaning drug regimen 06 is better at achieving better long-term cure. Various studies have shown that the addition of a bactericidal aminoglycoside (streptomycin) to isoniazid, rifampicin, and PZA is associated with higher sputum culture conversion after 2 months. The incidence of MDR and XDR TB is increasing worldwide as well as in Pakistan. According to various studies, primary drug resistance to streptomycin ranges from 5.4% to 19%. Our study was revived by the already proven fact that an aminoglycoside regimen is associated with a higher culture conversion rate. We have demonstrated this with a relatively new aminoglycoside, but the results are comparable to previous studies done with streptomycin-containing regimens.

An important consequence of our study is that with this treatment regimen 06 we are sufficiently confident that our patients are non-infectious after 2 months at most and are no longer a potential source of tuberculosis for the general public, close contacts and healthcare professionals. This regimen can be recommended for use in patients with risk factors for delayed culture conversion. This fact is of paramount importance in countries where bacteriological monitoring is not available or not routinely performed to reduce treatment costs, and in countries where the possibilities of airway isolation are very limited.

The limitations of our study include a smaller sample size, no calculation of the mean time from treatment to conversion of the culture, no analysis of risk factors for delayed conversion of the culture, and no follow-up of patients for more than two months. Therefore, we are unable to verify the long-term effects of the higher conversion rate of the cultures observed in our study. We recommend planning further studies on a larger sample, calculating the median time from treatment to conversion of the culture, and analyzing risk factors for delayed conversion of cultures, so that final recommendations for a treatment regimen can be made 06. We also recommend a long-term follow-up study to be verified the effect of culture conversion after 02 months on the relapse rate and long-term recovery.

CONCLUSION:

The addition of amikacin and levofloxacin to the standard ATT regimen is associated with a higher culture conversion rate after 2 months. The regimen containing amikacin and levofloxacin was not associated with any side effects and was well tolerated by patients. This regimen can be recommended for use in patients with risk factors for delayed culture conversion.

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