

Original Research Article

Effectiveness and safety of co-administration of moxifloxacin with netilmicin in drug-resistant tuberculosis patients, and its impact on inflammatory factors and immune function

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Abstract

Purpose: To study the effectiveness and safety of co-administration of moxifloxacin with netilmicin in drug-resistant tuberculosis (TB) patients, and its impact on levels of inflammatory factors and immune function.

Methods: We enrolled 100 patients with drug-resistant TB admitted to People's Hospital of Rizhao between May 2017 and October 2019. The patients were randomly allocated to control group and study group, with 50 patients per group. The control group received moxifloxacin at a dose of 0.2 g t.i.d. for 6 months and the study group received netilmicin at a dose of 0.1 g t.i.d. plus. The response, incidence of adverse reactions, expression levels of inflammatory factors, immune function, and sputum-negative status after 2, 4 and 6 months of TB treatment were compared.

Results: The study group showed markedly higher response than the control group ($p < 0.05$). Moreover, there were lower incidence of adverse effects in the study group than in the control group ($p < 0.05$). The expression levels of inflammatory factors were significantly lower in the study group, while the concentrations of CD3⁺, CD4⁺, and CD8⁺ were markedly higher ($p < 0.05$). After 2, 4 and 6 months of TB treatment, cases of sputum-negative conversion were significantly higher in the study group than in the control group ($p < 0.05$).

Conclusion: Co-administration of moxifloxacin with netilmicin produces much higher effectiveness and safety than moxifloxacin monotherapy, decreases inflammatory factor levels and improves immune function in patients with drug-resistant TB.

Keywords: Moxifloxacin, Netilmicin, Drug-resistant tuberculosis, Inflammatory factors, Immune function

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INTRODUCTION

Tuberculosis (TB) is a severe communicable lung disease attributable to *Mycobacterium tuberculosis* infection which is transmitted

primarily through the respiratory route. With constant advancements in medical technologies, certain antibiotics have been found to be of therapeutic potential for TB. However, frequent antibiotic use leads to drug resistance, resulting

in reduced susceptibility to *Mycobacterium tuberculosis* and reduction in drug effect [1-3]. Moxifloxacin, a fluoroquinolone antibiotic with potent antibacterial activity, is effective in patients with upper and lower respiratory tract infections. Besides, it is used clinically for treatment of TB patients [4-6]. However, clinical trials have demonstrated unsatisfactory therapeutic effect of moxifloxacin monotherapy on TB. Netilmicin exhibits good activity against *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterobacter spp.* and *Staphylococcus aureus*, as well as good antimicrobial activity [7,8].

In this retrospective study, the results of treatment strategies for drug-resistant TB patients were investigated. Patients in the control group were treated with moxifloxacin, while those in the study group were treated with moxifloxacin co-administered with netilmicin. Subsequently, the response, incidence of adverse effects, expression levels of inflammatory factors, immune function, and sputum-negative conversion status after 2, 4 and 6 months of TB treatment were compared.

METHODS

General patient profile

We enrolled 100 patients with drug-resistant TB admitted to *People's Hospital of Rizhao* between May 2017 and October 2019. The patients were randomly allocated to control group (n = 50) and study group (n = 50). Patients in the study group and the control group were aged 31 - 57 and 33 - 57 years, respectively. There were no statistically significant differences in sex, age, course of disease and other general characteristics between the two groups ($p > 0.05$, Table 1).

Inclusion/exclusion criteria

Inclusion criteria

Patients in the following categories were included: those whose conditions were consistent with clinical features of drug-resistant TB, patients aged ≤ 18 years, patients with no disease in major organs, and those who had no history of drug allergy, drug abuse, and unhealthy habits. The Ethics Committee of People's Hospital of Rizhao has approved and reviewed this study (Approved no. 2017RZ0834), and all the patients took part in the study voluntarily, and provided signed informed consent. The experiment was conducted under the Ethical Guidelines for Human Research [9].

Exclusion criteria

Patients without drug resistance, those allergic to antibiotics, and those with severe liver and kidney dysfunction, were excluded from the study.

Treatments

Patients in both groups were administered the following drugs: rifapentine (Shanghai International Pharmaceutical Co. Ltd; NMPA approval number: H10940165) at a dose of 600 mg daily twice a week; prothioisoniazid (Shenyang Hongqi Pharmaceutical Co. Ltd; NMPA approval no. H21022339) at a dose of 0.2 g *t.i.d.*, capreomycin (Zhejiang Hisun Pharmaceutical Co. Ltd; NMPA approval number: H20094030) at a dose of 0.5 g *b.i.d.*, and pasiniazide (Chongqing Huapont Pharm Co. Ltd; NMPA approval no. H50022019) at a dose of 0.5 g *b.i.d.* [10-12]. These drugs were continuously administered for 6 months, and then for 9 months after removal of capreomycin.

Table 1: Basic patient profile

Variable	Study group	Control	t/ χ^2	P-value
Sex (M/F)	22/28	24/26	0.16	0.69
Age (years)	44.36 \pm 4.51	44.19 \pm 4.07	0.20	0.84
Height (cm)	165.29 \pm 9.30	165.33 \pm 9.68	0.02	0.98
Weight (kg)	66.22 \pm 7.20	66.91 \pm 7.48	0.47	0.64
Medical history (M)	2.33 \pm 0.54	2.38 \pm 0.63	0.43	0.67
Smoking history (Y)	8.20 \pm 2.60	8.34 \pm 2.55	0.27	0.79
Alcohol history (years)	12.66 \pm 4.69	12.58 \pm 4.57	0.09	0.93
Drugs	Rifampicin	15	0.05	0.83
	Rimifon	17	0.18	0.67
	Ethambutol	10	0.51	0.48
	Pyrazinamide	8	0.33	0.56

Table 2: Comparison of response of both groups

Group	Significant	Effective	Ineffective	Overall response (%)
Study	30 (60)	16 (32)	4 (8)	46 (92)
Control	11 (22)	23 (46)	16 (32)	34 (68)
χ^2				9.00
P-value				0.003

Patients in the control group were given moxifloxacin (Beijing Bayer Healthcare Co. Ltd; NMPA approval number: J20100158) at a dose of 0.2 g *t.i.d.* for 6 months, and thereafter for 9 months after removal of capreomycin.

Patients in the study group were administered moxifloxacin intravenously for 1 hour at a dose of 0.2 g *t.i.d.* along with 0.1 g of netilmicin (Zhejiang Zhenyuan Pharmaceutical Co. Ltd; NMPA approval number: H10960309) diluted in 100 mL of physiological saline. The treatment lasted for 6 months, and thereafter for 9 months after removal of capreomycin and netilmicin.

Treatment indices

The response, incidence of adverse effects, expression levels of inflammatory factors, immune function, and sputum-negative conversion status after 2 months of TB treatment were assessed.

Treatment effect was regarded as *significant* if patient's TB symptoms completely disappeared, with recovery confirmed through test results; or *effective* if patient's TB symptoms were markedly reduced, with high degree of sputum-negative conversion, or *ineffective* if there were no significant reductions in the patient's TB symptoms, and no negative sputum test result.

Statistical analysis

Measurement data are displayed as mean \pm SD, and were subjected to statistical analysis using *t*-test. Enumeration data are presented as numbers and percentages [n (%)], and were analyzed using χ^2 test. All statistical analyses were done with SPSS 20.0, while GraphPad Prism7 (GraphPad Software, San Diego, USA) was used for graphics. Values of $p < 0.05$ indicated statistically significant differences.

RESULTS

Response

Patients in the study group showed markedly higher response than those in the control group ($p < 0.05$). These results are presented in Table 2.

Incidence of adverse effects

It was found that incidence of adverse effects (diarrhea, pruritus, and nausea) was markedly lower in the study group than in the control group ($p < 0.05$). These data are shown in Table 3.

Table 3: Comparison of incidence of adverse effects

Group	Diarrhea	Pruritus	Nausea	Overall incidence (%)
Study	2	2	1	10
Control	5	7	4	32
χ^2				7.29
P-value				0.007

Expression levels of inflammatory factors

Normal TNF- α and IL-6 ranged from 740 to 1540 and 56.37 to 150.33 pg/mL, respectively. Figure 1 shows lower serum expression levels of TNF- α and IL-6 in the study group than in the control group ($p < 0.05$).

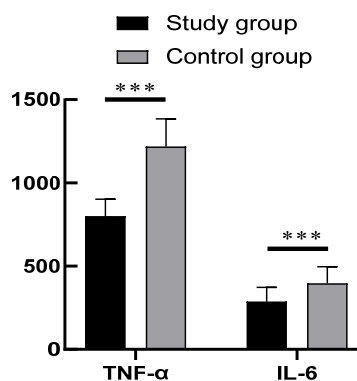


Figure 1: Relative expression levels of inflammatory factors. The serum TNF- α was (801.16 \pm 100.23 pg/mL) in the study group and (1217.53 \pm 166.89 pg/mL) in the control group; The serum IL-6 was (286.37 \pm 86.77 pg/mL) in the study group and (397.05 \pm 99.67 pg/mL) in control group. *** indicated $P < 0.001$

Immune function

High levels of CD3+, CD4+ and CD8+ in patients signified strong immune function. The immune function was judged by the contents of CD3+,

CD4+ and CD8+ in patients. As shown in Table 4, the levels of CD3+, CD4+, and CD8+ in the study group were significantly higher than the corresponding levels in the control group ($p < 0.05$).

Table 4: Comparison of immune functions

Group	CD3 ⁺	CD4 ⁺	CD8 ⁺
Study	879.62±116.57	488.05±86.21	471.55±86.71
Control	704.26±100.55	353.63±72.19	338.70±74.18
T	8.05	8.45	8.23
P-value	<0.001	<0.001	<0.001

Sputum-negative conversion (%) after 2, 4 and 6 months of treatment

The percentages sputum-negative conversion after 2, 4, and 6 months of treatment were significantly higher in the study group than in the control group ($p < 0.05$). These results are presented in Table 5.

Table 5: Sputum-negative conversion after 2, 4 and 6 months of treatment [n, (%)]

Group	2 months of treatment	4 months of treatment	6 months of treatment
Study	12 (24)	30 (60)	46 (92)
Control	2 (4)	16 (32)	33 (66)
χ^2	8.31	7.89	10.19
P-value	0.004	0.005	0.001

DISCUSSION

Mycobacterium tuberculosis spreads to multiple parts of the body and triggers infection of the respiratory system, followed by pulmonary infection, ultimately leading to TB. Ordinarily, malnourished and immuno-compromised elderly people are highly prone to infection with *Mycobacterium tuberculosis* [13-15].

Currently, various antibiotics such as isoniazid and rifampicin are generally necessary for the clinical treatment of TB. However, the sensitivity of *Mycobacterium tuberculosis* to drugs gradually decreases with long-term use of antibiotics, ultimately resulting in drug resistance. Once antibiotic resistance emerges, doctors need to change the antibacterial agents being used. Studies have shown that concomitant administration of multiple drugs is more effective in the treatment of TB than monotherapy, and inflammatory factors in patients reduce sharply after combination treatment [16-18].

In order to investigate a more suitable treatment for patients with drug-resistant TB, this study used a combination of moxifloxacin and netilmicin, and analyzed the differences in the expression levels of serum inflammatory factors, as well as immune function, response, and adverse effects between patients treated with concurrent administration of moxifloxacin and netilmicin, and those treated with moxifloxacin alone.

The results of this study indicate that the study group had markedly higher response than the control group. It was shown that the combination of moxifloxacin with netilmicin markedly improved response and promoted the sputum-negative conversion in patients. Moreover, there were markedly lower incidence of adverse effects and expression levels of inflammatory factors in the study group than in the control group.

It was further indicated that moxifloxacin-netilmicin combination markedly reduced the incidence of adverse effects, produced much higher safety, and markedly downregulated the expressions of inflammatory factors in patients and their inflammatory manifestations, thereby enhancing the treatment of TB. Moreover, concomitant administration of moxifloxacin and netilmicin in patients potently enhanced their immunity and reduced the risk of infection with other infectious diseases, while facilitating sputum-negative conversion and shortening the duration of treatment.

In a study conducted by Irfan *et al* [19], it was demonstrated that netilmicin in combination with levofloxacin achieved favorable effects in patients with drug-resistant TB, facilitated sputum-negative conversion, and improved therapeutic effects. It has been suggested that moxifloxacin is more clinically effective than levofloxacin in patients with drug-resistant TB, due to reduced incidence of adverse effects [20]. The results obtained in this study are consistent with these findings, indicating the scientific reliability of the conclusions in this study.

Limitations of the study

This study included a relative smaller sample size, and the generality of these results should be interpreted with caution concerning the clinical efficacy of moxifloxacin with netilmicin. In addition, this study is a single-center study, no blind method is used, and the follow-up time is shorter. Hence, the results need to be further

confirmed by a larger sample and multi-center study.

CONCLUSION

Concurrent administration of moxifloxacin and netilmicin in patients with drug-resistant TB markedly improves response, decreases incidence of adverse effects, downregulates expressions of inflammatory factors, enhances immune functions, and facilitates sputum-negative conversion. Thus, moxifloxacin-netilmicin combination treatment may be of high clinical value in patients with drug-resistant TB.

DECLARATIONS

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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