Clinical efficacy of the combined use of levofloxacin and different courses of isoniazid and rifampicin in the treatment of mild spinal tuberculosis

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**Abstract**

**Purpose:** To investigate the clinical effectiveness of the combined use of levofloxacin and different courses of isoniazid and rifampicin in the treatment of mild spinal tuberculosis (TB).

**Methods:** The clinic data of 100 patients with light spinal TB were retrospectively reviewed. A double-blind technique was used to divide the patients into 6-month treatment group (M6 group, n = 32), 12-month treatment group (M12 group, n = 34) and 18-month treatment group (M18 group, n = 34). All patients were given isoniazid and rifampicin, in combination with levofloxacin. The effects of the different treatment courses on mild spinal TB were determined.

**Results:** There were significantly higher post-treatment levels of inflammatory factors in M6 group than in M12 and M18 groups (p < 0.001). Moreover, there were significantly higher Visual Analogue Scale (VAS) score and erythrocyte sedimentation rate (ESR), and larger focus size in M6 group than in M12 and M18 groups (p < 0.05). However, after treatment, M18 group had significantly higher total incidence of adverse reactions than M6 and M12 groups (p < 0.05).

**Conclusion:** Compared with the short-course treatment, long-course treatment with isoniazid and rifampicin in combination with levofloxacin is more effective in reducing the levels of inflammatory factors and decreasing focus size in patients with mild spinal TB. However, patients given the 18-month treatment tend to develop more adverse reactions. Therefore, 12-month treatment with the combined therapy is a better therapeutic option.

**Keywords:** Mild spinal tuberculosis, Isoniazid, Rifampicin, Levofloxacin, Varied treatment courses, Clinical efficacy

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**INTRODUCTION**

Tuberculosis (TB) is one of the infectious diseases that jeopardize human health, and one of the top 10 causes of death due to a single infectious disease worldwide [1]. The disease is caused by *Mycobacterium tuberculosis* infection, and it affects almost all organs and tissues in the
body. Patients with bone and joint TB account for about 5 - 10 % of all TB subjects, while patients with spinal TB account for about 55 % of those with bone and joint TB, with the spine being the most dangerous infection site [2]. Spinal TB often leads to cold abscesses, destruction of spinal bone and spinal deformity, eventually resulting in paraplegia and poor quality of life [3]. Due to the complexity of the disease, different courses of isoniazid have been demonstrated in elderly patients with endobronchial TB [5]. Rifampicin is the most effective bactericide used in anti-TB treatment programs for eradication of mycobacteria. Although the currently-used TB treatment programs produce significant curative effects, there is still need for enhancement of their overall therapeutic effectiveness [6,7]. It has been reported that levofloxacin exerts its antibacterial effect by inhibiting the gyrase activity of Mycobacterium tuberculosis DNA [8]. However, there are many controversies about drug treatments for mild spinal TB, and no consensus has been reached. The present study was conducted as a retrospective analysis to investigate the effects of the combination of levofloxacin with different courses of isoniazid and rifampicin on mild spinal TB, in order to provide evidence-based data for improving TB treatment programs.

METHODS

General biodata of patients

The clinical data of 100 patients with mild spinal TB treated at The First Affiliated Hospital of Xinxiang Medical University from March 2015 to March 2020 were retrospectively reviewed. A double-blind technique was used to divide the patients into 6-month treatment group (M6 group, n = 32), 12-month treatment group (M12 group, n = 34) and an 18-month treatment group (M18 group, n = 34). The study was approved by the ethics committee of The First Affiliated Hospital of Xinxiang Medical University (approval no. 20180101), and was carried out in line with the principles of Declaration of Helsinki [9]. Signed written informed consent was obtained from the patients and/or guardians.

Isoniazid, a frequently-used anti-TB drug in clinics, exerts highly selective antibacterial effects on various strains of Mycobacterium tuberculosis [4]. Moreover, the effectiveness of isoniazid has been demonstrated in elderly patients with endobronchial TB [5]. Rifampicin is the most effective bactericide used in anti-TB treatment programs for eradication of mycobacteria. Although the currently-used TB treatment programs produce significant curative effects, there is still need for enhancement of their overall therapeutic effectiveness [6,7]. It has been reported that levofloxacin exerts its antibacterial effect by inhibiting the gyrase activity of Mycobacterium tuberculosis DNA [8]. However, there are many controversies about drug treatments for mild spinal TB, and no consensus has been reached. The present study was conducted as a retrospective analysis to investigate the effects of the combination of levofloxacin with different courses of isoniazid and rifampicin on mild spinal TB, in order to provide evidence-based data for improving TB treatment programs.

Inclusion and exclusion criteria

Inclusion criteria

Patients in the following categories were included: those whose pathologic findings under CT-guided needle biopsy confirmed TB infection, with histopathological results from specimen biopsies displaying tuberculous granulomas and caseous necrotic tissues; patients with imaging and clinical manifestations consistent with diagnosis of spinal TB to the exclusion of other diseases; and patients who met the diagnostic criteria for mild spinal TB, i.e., mild bone destruction (< 1/3 vertebral body height), absence of neurological dysfunction, absence of obvious kyphotic deformity (Cobb angle < 30°), and no evidence of obvious intervertebral destabilization.

Exclusion criteria

The excluded subjects were patients who could not cooperate with the researchers during the study due to disorders in consciousness or mental disorders, patients suffering from severe hepatic or renal dysfunction, and subjects with complications of respiratory diseases.

Treatments

The patients were given different treatment programs depending on their groups: 2SHRZ/4HRE (M6 group), 2SHRZ/10HRE (M12 group), and 2SHRZ/10HRE/6HR (M18 group). The identities of the drugs, and their doses (in brackets) were: S for streptomycin (0.75 g/day); H for isoniazid (0.3 g/day); R for rifampicin (0.45 g/day for body weight < 60 kg, or 0.6 g/day for body weight ≥ 60 kg); Z for pyrazinamide (1 g/day); and E for ethambutol (0.75 g/day). The patients received S via intramuscular injection, while Z was administered orally 3 times daily. The other drugs were administered early in the morning.

In addition, patients in the three groups were orally given 0.2 g of levofloxacin (Daiichi Sankyo Company Limited; NMPA Approval no. H20000655; specification: 0.1 g × 10 tablets/box) 3 times a day. Patients in M6, M12 and M18 groups were continuously treated with levofloxacin for 6, 12 and 18 months, respectively.

Evaluation of parameters/indices

At the end of each treatment period, 4 mL of fasting venous blood was drawn from each patient in the morning. The blood sample was
used for the determination of erythrocyte sedimentation rate (ESR) using the Westergren method. Serum levels of C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were determined with enzyme-linked immunosorbent assay (ELISA) kits in line with the manufacturer’s protocols.

The Visual Analogue Scale (VAS) [10] was used to assess the levels of post-treatment pain in patients. Rather than filling out a complicated questionnaire, the patients only needed to look at the pain scale and indicate a number between 0 and 10 as an index of degree of pain being felt. The higher the scores, the more severe the pain.

Computed Tomography (CT) was used to evaluate post-treatment focus size. Adverse reactions during treatment were recorded.

### Statistical analysis

The professional statistical software, SPSS version 26.0, was used for data processing, while GraphPad Prism 7 (GraphPad Software, San Diego, USA) was used for preparation of graphs. Count data are expressed as numbers and percentages (n (%)); statistical comparison was done using chi squared ($\chi^2$) test. Measurement data are presented as mean ± SD, and comparison was done using Student’s t-test. Values of $p < 0.05$ were considered indicative of statistically significant differences.

### RESULTS

#### General patient data

There were no significant differences amongst the three groups, with respect to general data such as age, lesion location and level of destruction of vertebral body ($p > 0.05$; Table 1).

#### Levels of inflammatory factors

Post-treatment levels of inflammatory factors were significantly higher in M6 group than in M12 and M18 groups ($p < 0.001$). These results are shown in Table 2.

#### VAS score

After treatment, M6 group had significantly higher VAS score than M12 and M18 groups ($p < 0.05$; Figure 1).

#### Erythrocyte sedimentation rate (ESR)

Post-treatment value of ESR was significantly higher in M6 group than in M12 and M18 groups ($p < 0.05$; Figure 2).

### Table 1: Comparison of general data amongst the 3 groups (mean ± SD)

| Parameter                              | M6 group (n=32) | M12 group (n=34) | M18 group (n=34) | $\chi^2$/t | P-value |
|----------------------------------------|-----------------|------------------|------------------|------------|---------|
| Sex                                    |                 |                  |                  | 0.991      | 0.474   |
| Male/Female                            | 14/18           | 15/19            | 20/14            |            |         |
| Body mass index (kg/m$^2$)             | 22.00±1.51      | 22.07±1.47       | 21.89±1.39       | 0.339      | 0.738   |
| Age (years)                            | 46.69±5.41      | 46.71±5.03       | 45.76±5.83       | 0.469      | 0.656   |
| Disease course (months)                | 6.91±3.80       | 7.38±3.59        | 7.65±3.77        | 0.538      | 0.600   |
| Lesion location                        |                 |                  |                  |            |         |
| Thoracic vertebra                      | 9 (28.13)       | 11 (32.35)       | 10 (29.41)       | 0.074      | 0.803   |
| Thoracolumbar spine                    | 7 (21.88)       | 10 (29.41)       | 11 (32.35)       | 0.220      | 0.676   |
| Lumbar vertebra                        | 16 (50.00)      | 13 (38.24)       | 13 (38.24)       | 0.617      | 0.557   |
| **American spinal injury association (ASIA) Classification** |                 |                  |                  |            |         |
| Grade A                                | 3 (9.38)        | 2 (5.88)         | 4 (11.76)        | 0.370      | 0.577   |
| Grade B                                | 2 (6.25)        | 4 (11.76)        | 3 (8.82)         | 0.307      | 0.606   |
| Grade C                                | 8 (25.00)       | 9 (26.47)        | 8 (23.53)        | 0.039      | 0.853   |
| Grade D                                | 8 (25.00)       | 6 (17.65)        | 10 (29.41)       | 0.657      | 0.461   |
| Grade E                                | 11 (34.38)      | 13 (38.24)       | 9 (26.47)        | 0.556      | 0.517   |
| **Level of destruction of vertebral body** |                 |                  |                  |            |         |
| Mild                                   | 23 (71.88)      | 22 (64.71)       | 23 (67.65)       | 0.199      | 0.680   |
| Moderate                               | 6 (18.75)       | 8 (23.53)        | 5 (14.71)        | 0.425      | 0.550   |
| Severe                                 | 3 (9.38)        | 4 (11.76)        | 6 (17.65)        | 0.509      | 0.525   |
| **Place of residence**                 |                 |                  |                  | 0.165      | 0.738   |
| Urban area                             | 14 (43.75)      | 15 (44.12)       | 17 (50.00)       |            |         |
| Rural area                             | 18 (56.25)      | 19 (55.88)       | 17 (50.00)       |            |         |
Table 2: Comparison of levels of inflammatory factors amongst the 3 groups (mean ± SD)

| Group | n  | CRP (mg/L)       | IL-6 (pg/mL) | TNF-α (pg/mL) |
|-------|----|------------------|--------------|---------------|
| M6    | 32 | 22.28±4.82       | 20.30±1.35   | 20.96±2.33    |
| M12   | 34 | 12.69±3.06 *     | 9.46±1.02 *  | 9.12±0.68 *   |
| M18   | 34 | 11.62±2.99 **    | 9.11±1.04 ** | 8.90±0.93 **  |

* P < 0.05, levels of CRP, IL-6 and TNF-α in M6 group vs levels of CRP, IL-6 and TNF-α in M12 group; **P < 0.05, levels of CRP, IL-6 and TNF-α in M6 group vs levels of CRP, IL-6 and TNF-α in M18 group.

DISCUSSION

Spinal TB has the highest incidence (50%) among all types of systemic bone and joint TB. Spinal TB occurs mostly in the vertebral body, and it often involves the intervertebral disc, thereby resulting in the destruction of vertebral body and narrow intervertebral space [11].

As a result, the affected patients may develop a variety of corresponding clinical symptoms. Although the current TB treatment programs and drugs have benefited from gradual improvements, TB still poses a serious harm to human health worldwide. With approximately 1.45 million newly diagnosed cases each year, China is one of the countries with a high incidence of TB in the world [12]. Besides, in China, TB-related deaths are top in the list of deaths caused by infectious diseases [13].

The respiratory system is the point through which TB enters the body. From the respiratory system, it may progress to pulmonary TB, and may also spread to other tissues and organs through the circulatory system [14].

Table 3: Comparison of adverse reactions after treatment (n (%))

| Group | n  | Peripheral neuropathy | Aplastic anemia | Limb pain | Epigastric discomfort | Insomnia | Total incidence |
|-------|----|-----------------------|-----------------|-----------|-----------------------|----------|-----------------|
| M6    | 32 | 0 (0)                 | 1 (3.13)        | 2 (6.25)  | 1 (3.13)              | 1 (3.13) | 15.63% (5/34)   |
| M12   | 34 | 1 (2.94)              | 1 (2.94)        | 3 (8.82)  | 1 (2.94)              | 1 (2.94) | 20.59% (7/34)   |
| M18   | 34 | 3 (8.82)              | 2 (5.88)        | 3 (8.82)  | 3 (8.82)              | 2 (5.88) | 38.24% (13/34)  |
Spinal TB impairs neurological function and causes paraplegia in the patient. These complications seriously affect physical and mental health of the affected patients, and also impose heavy economic and psychological burdens on the subjects and their families. From initial helplessness to successful development of isoniazid, it is obvious that the treatment for spinal TB has undergone significant changes. The continued discovery of more anti-TB drugs, and the development of evidence-based medicine make the treatment programs more scientific and more standardized. Indeed, drug use has become the main treatment strategy for mild spinal TB [15].

Isoniazid, the most common medication among the anti-TB drugs, inhibits the synthesis of nucleic acid in Mycobacterium tuberculosis and effectively enhances the rupture of cell walls. It has been reported that isoniazid produced significant curative effect in patients with TB-associated meningitis [16]. Rifampicin, a core anti-TB drug, is the most effective bactericide in the TB treatment programs. Rifampicin kills both actively dividing and dormant Mycobacteria, and it is also very effective against pneumoconiosis TB [17]. Levofloxacin, a third-generation quinolone, has wide spectrum of antimicrobial effect, and it is frequently used for treating urinary tract infections. The in vitro antibacterial activity of levofloxacin is twice stronger than that of ofloxacin, and it inhibits the synthesis and replication of bacterial DNA by suppressing the activity of bacterial DNA gyrase. In this way, levofloxacin exerts its antibacterial effect [18]. At present, there are no studies on the clinical effectiveness of combined use of levofloxacin with different courses of isoniazid and rifampicin in the treatment of mild spinal TB.

This study reviewed the records of patients with mild spinal TB treated in The First Affiliated Hospital of Xinxiang Medical University from March 2015 to March 2020, in order to provide evidence-based strategy for improving clinical treatment effectiveness. The results obtained showed that the levels of inflammatory factors in patients given 12-month and 18-month drug treatments were lower than the corresponding levels in patients subjected to 6-month drug treatment. These results suggest that the combined use of levofloxacin and various courses of isoniazid and rifampicin effectively reduced inflammatory response in patients with mild spinal TB, with better clinical effectiveness in long-course treatment than in short-course treatment. This is likely due to the fact that since spinal TB tends to progress to fibrotic lesions, the resultant sparse capillaries and poor blood supply in the local focus make it difficult for the local plasma drug concentration to reach the minimum bactericidal concentration. Under prolonged stimulation by low plasma drug concentration, more and more Mycobacterium tuberculosis get converted to B and C microflora which require extended course of treatment to eliminate [19].

Erythrocyte sedimentation rate (ESR) is one of the most conventional laboratory indices used for diagnosis of spinal TB [20]. In this study, after treatment, M6 group had higher ESR than M12 and M18 groups. This is an indication that the long-course treatment program reduced ESR, thereby exerting positive effect on the patients. Patients in M18 group had significantly higher total incidence of adverse reactions than those in M6 group and M12 groups, indicating that although the long-course treatment program had better effects with respect to reduction of inflammatory response and ESR, when compared to the short-course treatment program, it brought many adverse reactions. Therefore, 12-month treatment program produced better treatment effect on mild spinal TB in terms of reduction of adverse reactions. Levofloxacin is known to be effective, but its feasibility and long-term efficacy as a second-line anti-TB drug when used in single application for treating mild spinal TB are controversial.

Limitations of the study

Although the study data were accumulated over a period of five years, the sample size used was small. This limitation might lead to statistical bias. Moreover, this study did not involve long-term, post-treatment follow-up of the patients for continued monitoring of treatment effectiveness. Thus, the study did not monitor the effects of drug treatment programs on long-term clinical efficacy. Therefore, in subsequent studies, the experimental design should be improved and the sample size should be enlarged so as to confirm the findings in this research.

CONCLUSION

This study has demonstrated that, compared with the short course of treatment, combined long-course use of levofloxacin and different courses of rifampicin and isoniazid effectively reduce the levels of inflammatory factors and shrink the focus in patients with mild spinal TB. However, patients subjected to 18-month treatment tend to develop more adverse reactions than those given 12-month treatment. Therefore, the 12-month combined therapy may be recommended for mild spinal TB patients after further studies using a
larger sample size to confirm treatment outcomes.

DECLARATIONS

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Ethical approval

The study was approved by the ethics committee of The First Affiliated Hospital of Xinxiang Medical University (approval no. 20180101).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest 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. Xuanyu Chen, Mingxing Cui and Xiang Ji conceived and designed the study, and drafted the manuscript. Xuanyu Chen, Kaifeng Jin, Hui Zhao, Weitao Zhong, Zhenhua Zhang, Liming Zhang, Yuankun Geng, Aizhen Yang and Ying Zhao collected, analyzed and interpreted the experimental data. Mingxing Cui, Xiang Ji and Kaifeng Jin revised the manuscript for important intellectual content. All authors read and approved the final manuscript. Xuanyu Chen and Mingxing Cui contributed equally to this article.

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