Comparison of efficacy and safety of two fixed-dose combination regimens for tuberculosis in the Chinese population

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SUMMARY

To date, there have been few studies on the dosage of fixed-dose combination (FDC) for the treatment of tuberculosis (TB) in the Chinese population. The aim of this study was to evaluate the efficacy and safety of two FDC regimens in two provinces with a high tuberculosis burden. A total of 2,353 newly diagnosed active pulmonary TB patients were recruited from Shandong Province (n=1,223) and Jilin Province (n=1,130). Participants received FDC treatment for six months (intensive phase and continuation phase). The difference in the two regimens was the dosage of FDC in the continuation phase. For Shandong Province, the cure rate was 96.4% (370/384). In all, 1,172 patients successfully completed the treatment, the success rate being 95.8% (1,172/1,223). For Jilin Province, the cure rate was 92.5% (345/373): 1,109 patients successfully completed the treatment and the treatment success rate was 98.1% (1,109/1,130). Significant differences were observed in the cure rate (χ^2=5.382, p=0.020) and the treatment success rate (χ^2=10.581, p=0.001) between the two provinces. The integral analysis showed that both regimens had similar efficacy, but the regimen of Jilin Province was inferior to that of Shandong Province in terms of safety.

Keywords: Fixed-dose combination; anti-tuberculosis drug; clinical effect.

INTRODUCTION

Tuberculosis (TB) remains a major cause of morbidity and mortality around the world, with about 9.6 million new incident cases and 1.5 million deaths annually. Although TB occurs in many countries, Indonesia, India and China have the highest number of cases, accounting for 43% of the global burden [1]. China is a country with the second large TB burden in the world [2]. World Health Organization (WHO) reported the number of TB patients in China was about 1.4 million and its estimated prevalence was 102/100,000, the estimated incidence 73/100,000, and the mortality 2.9/100,000 in 2014 [3]. After 20 years of efforts, TB incidence begins to reverse, but the incidence of multidrug-resistant TB (MDR-TB) continues to rise [4,5]. Moreover, HIV has greatly increased the risk of latent TB infection developing to active disease in co-infected individuals, and has led to a significant TB epidemic in many countries [6]. Therefore, TB is a major public health problem and socioeconomic threat [7].

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TB is treatable and curable, but without proper treatment, up to two-thirds TB patients will die [8]. For newly diagnosed cases, the previous regimen was a standard six months course of four antimicrobial drugs, taking more than ten pills each time. It was related to poor compliance which led to resistant strains and multidrug resistant bacilli. Until 1994, WHO and the International Union Against Tuberculosis and Lung Diseases (IUATLD/ The Union) recommended the use of fixed-dose combination (FDC) drug formulations to cure pulmonary TB [7]. FDCs are anti-tuberculosis (anti-TB) drugs that contain two or more basic TB drugs in the same tablet and prevent the development of drug resistance. FDC can simplify the prescription, make dispensing easier, reduce pill burden and risk of improper dosing, ensure patient acceptability, and avoid inappropriate monotherapy or misusing [6, 9]. China began to use FDC in the early 1990s, and plans to use it as an alternative to anti-TB blister pack drug, and as a national program of anti-TB drug during the period of "13rd Five-Year Plan". Although numerous studies have shown that FDCs are effective to treat TB, there are few studies on the dosage of FDC in the Chinese population. Therefore, it is very important to carry a research about the dosage of FDC that suits Chinese population.

The aim of this study was to assess the efficacy and safety of two regimens, and to select the better one through comparing improvement of clinical symptoms, adverse drug reaction, and patient compliance. In this regard, this study may be useful to help to choose a more appropriate FDC regimen for treatment of pulmonary TB that can be widely used in China.

PATIENTS AND METHODS

Study Population

Between July 1st, 2011 and December 31st, 2012, a total of 2,353 newly diagnosed active pulmonary TB patients were recruited from Shandong Province (n=1,223) and Jilin Province (n=1,130). The exclusion criteria were:

1) pregnant women;
2) patients with drug resistance or drug allergy;
3) patients younger than 15 years old;
4) patients with body weight less than 30 kg;
5) patients with severe hepatic and renal dysfunction and mental disorders.

Study regimens

The FDC regimen of Shandong Province is a 2-month regimen of daily rifampicin, isoniazid, pyrazinamide and ethambutol, followed by a

Table 1 - Doses of drugs used in the trial.

Province	*Phase*	*Dose by Body Weight, No. of Tablets*			
		30-37 kg	*38-54 kg*	*55-70 kg*	*≥70 kg*
Shandong	Intensive Combined tablet (HRZE) Isoniazid (150 mg) Rifampicin (75 mg) Pyrazinamide (400 mg) Ethambutol (275 mg)	2	3	4	5
	Continuation Combined tablet (HR) Isoniazid (150 mg) Rifampicin (300 mg)	2	2	2	2
Jilin	Intensive Combined tablet (HRZE) Isoniazid (150 mg) Rifampicin (75 mg) Pyrazinamide (400 mg) Ethambutol (275 mg)	2	3	4	5
	Continuation Combined tablet (HR) Isoniazid (200 mg) Rifampicin (200 mg)	3	3	4	4

4-month phase of continuation with daily rifampicin and isoniazid. The FDC regimen of 2-month of intensive phase in Jilin Province is the same as Shandong Province, and followed by a 4-month phase of continuation with rifampicin and isoniazid every other day.

The doses of drugs were given according to recommendations from the anti-tuberculosis fixed-dose combination manual of China (Table 1) and based, for each patient, on the pre-treatment weight. Subsequent doses did not adjust for weight change during treatment. One month of intensive phase was added when smear-positive sputum specimens of patients did not convert into smear-negative ones after 2-months of intensive treatment.

Clinical measurements

Before treatment, an anthropometer was used to measure the weight. A detailed questionnaire including socio-demographic characteristics, compliance of patients, drug substitution and Adverse Drug Reaction (ADR) was investigated by researchers for each subject. Additional information was collected from available medical records.

Follow-up

Compliance questionnaires were implemented before treatment, after the initial intensive phase and after treatment. Patients were interviewed for ADR at the end of each month of treatment. The sputum-smears were measured at pre-treatment, 2, 3, 5 and 6 months of treatment. Patients who forgot the time of follow-up were contacted through a home visit or telephone conversation by a trial coadjutant and asked to return to the study clinic.

Definitions

Drinking history was defined as drinking more than four times per week on average, including spirits, beer, wine, or other alcohol or/and consumption of at least 50 g pure alcohol. The severity of adverse drug reaction was divided into mild (may slightly affect patient's normal function), moderate (need to conduct symptomatic treatment or withdrawal), severe (based on one or more of the following components:

a) cause death;
b) may lead to carcinoma, malformation, and birth defects;
c) may endanger patient's health or cause disability;
d) may produce permanent impairment or incapacitation of organ functioning;
f) may cause hospitalization or prolong the time of hospitalization.

Cure rate (also called sputum negative conversion rate) was defined as the number of patients with sputum smear-negative at the end of treatment divided by the number of patients with sputum smear-positive before the treatment. Treatment completion was defined as completion of treatment without meeting the cure or failure criteria. Treatment success was defined as the sum of cure and treatment completion. Distance was defined as the kilometers from home to local hospital. Cost was defined as the cost of one-way transportation by public transport.

Ethics statement

This study was approved by the ethics committee of Chinese Center for Disease Control and Prevention and Public Health School of Jilin University (Changchun China). Written informed consent was provided by all participants or their surrogates before enrolment.

Statistical analysis

All data analyses were performed using IBM SPSS 24.0 software. Categorical variables were examined using Chi-squared test or Fisher's exact test. Continuous variables were examined using Student's t-test. P-values were two-tailed, and a p-value of <0.05 was considered to statistically significance.

RESULTS

Study population

The characteristics of patients are reported in Table 2. A total of 2,353 patients were included in this study, of which, 1,223 patients were from Shandong Province (52.0%) and 1,130 patients were from Jilin Province (48.0%). The average age of Shandong Province and Jilin Province was 48.60±18.71 years and 43.89±15.87 years, respectively. The average weight of patients from two provinces was 58.01±13.38 kg and 58.30±7.56 kg, respectively. The distance of patients from Shandong Province and Jilin Province from home to hospital was 19.85±15.45 kilometers and

Table 2 - Demographic characteristics of Shandong and Jilin Province of China.

Variables	*Shandong, n (%)*	*Jilin, n (%)*
Total	1223	1130
Gender (male)	905 (74.1)	801 (71.1)
Age, years		
~18	30 (2.5)	58 (5.2)
19~44	457 (38.0)	487 (43.3)
45~59	296 (24.6)	402 (35.7)
60~	419 (34.9)	178 (15.8)
Ethnicity (Han)	1216 (99.6)	1107 (98.2)
Occupation		
Manual workers	1070 (87.6)	898 (79.7)
Mental workers	92 (7.5)	99 (8.8)
Unemployed	43 (3.5)	118 (10.5)
Retired	17 (1.4)	12 (1.1)
Level of education		
Below primary school	370 (30.3)	69 (6.2)
Primary school	312 (25.5)	339 (30.2)
Junior high school	321 (26.2)	502 (44.8)
Senior high school	126 (10.3)	151 (13.5)
Junior college and above	94 (7.7)	60 (5.4)
Marital status		
Never married	242 (19.8)	257 (22.8)
Married or cohabit	918 (75.1)	833 (73.9)
Divorced or widowed	63 (5.2)	37 (3.3)
Medicare (Yes)	1097 (90.2)	1007 (91.1)
Allergy (Yes)	35 (2.9)	24 (2.1)
Drinking (Yes)	338 (27.8)	220 (19.7)
Sputum smear microscopy (Negative)	838 (68.6)	755 (66.9)
Complications (Yes)	108 (8.9)	28 (2.5)
Comorbidities (Yes)	51 (4.2)	60 (5.4)

30.31±21.15 kilometers, respectively. The average cost of the study subjects from Shandong Province was 6.65±4.51 yuan, the average cost of the study subjects from Jilin Province was 11.09±13.44 yuan.

Efficacy of therapy on tuberculosis

The results of sputum negative conversion after intensive treatment are presented in Table 3. The sputum negative conversion rate of Shandong Province and Jilin Province was 97.4% (374/384) and 100.0% (373/373) at the end of intensive treatment, respectively. There was a significant difference in sputum negative conversion rate after intensive treatment between Shandong Province and Jilin Province (χ^2=7.94, p=0.005).

Treatment outcomes for patients with pulmonary TB are showed in Table 4. For Shandong Province, the curing rate was 96.4% (370/384). The 1,172 patients successfully completed the treatment and the treatment success rate was 95.8% (1,172/1,223). For Jilin Province, the curing rate was 92.5% (345/373). The 1,109 patients successfully completed the treatment and the treatment success rate was 98.1% (1,109/1,130). Additionally, the significant differences were observed in the curing rate (χ^2=5.382, p=0.020) and the treatment success rate (χ^2=10.581, p=0.001) between the two provinces.

Adverse events

The common adverse reactions are summarized in Table 5. The incidence of adverse reactions in Shandong Province and Jilin Province was 6.3% (77/1,223) and 12.4% (140/1,130), respectively. A significant difference in adverse reactions was found between two provinces (χ^2=26.193, p<0.001). Digestive system was the most frequently reported adverse reaction in two provinces (4.25% in Shandong Province; 10.27% in Jilin Province). Similarly, patients with moderate

Table 3 - Situation of the sputum negative conversion after intensive treatment.

Province	*N*	*Two months*		χ^2	*p*	*Three months*		χ^2	*p*
		Negative sputum n (%)	*Positive sputum n (%)*			*Negative sputum n (%)*	*Positive sputum n (%)*		
Shandong	384	353 (91.9)	31 (8.1)	21.028	<0.001	374 (97.4)	10 (2.6)	7.947	0.005
Jilin	373	369 (98.9)	4 (1.1)			373 (100.0)	0 (0.0)		

Table 4 - Treatment outcome of standardized therapy between Shandong Province and Jilin Province.

Province	*N*	*Cure n (%)*	*Treatment Completion n (%)*	*Death of tuberculosis n (%)*	*Death of Non-tuberculosis n (%)*	*Failure n (%)*	*Missing n (%)*	*Others n (%)*
Shandong	1223	370 (30.3)	802 (65.6)	3 (0.2)	15 (1.2)	2(0.2)	7 (0.6)	24 (2.0)
Jilin	1130	345 (30.5)	764 (67.6)	1 (0.1)	3 (0.3)	3 (0.3)	6 (0.5)	8 (0.7)

Table 5 - Number of adverse reactions occurred in the most common systemic diseases n (%).

Adverse symptoms	*Adverse reactions*		*Moderate and severe adverse reactions*	
	Shandong	*Jilin*	*Shandong*	*Jilin*
Digestive system	52 (4.3)	116 (10.3)	48 (3.9)	15 (1.3)
Nervous system	9 (0.7)	93 (8.2)	9 (0.7)	10 (0.9)
Urinary system	2 (0.2)	4 (0.4)	2 (0.2)	2 (0.2)
Arthrosis	1 (0.1)	9 (0.8)	0 (0.0)	2 (0.2)
Allergic reaction	20 (1.6)	48 (4.2)	18 (1.5)	8 (0.7)

Table 6 - Treatment outcome of standardized therapy for TB patients with and without compliance.

Compliance	*Province*	*N*	*Smear-positive**	*Cure N (%)*	*Effective n (%)*
No	Shandong	47	14	3 (21.43)	8 (17.02)
	Jilin	40	16	14 (87.50)	33 (82.50)
	χ^2	–	–	13.274	17.618
	p	–	–	<0.001	<0.001
Yes	Shandong	1176	370	367 (99.19)	1164 (98.98)
	Jilin	1090	357	331 (92.72)	1076 (98.72)
	χ^2	–	–	19.872	0.348
	p	–	–	<0.001	0.555

*smear-positive means the number of smear-positive before the treatment in different groups

and severe adverse reactions mainly occurred in digestive system (3.92% in Shandong Province; 1.33% in Jilin Province).

Compliance investigation

No significant differences were found in the compliance of patients between two provinces (p>0.05). At the end of the intensive treatment, 97.1% (1,188/1,223) patients were able to adhere to treatment for the next 4 months in Shandong Province and 98.1% (1,108/1,130) in Jilin Province. 76.7% (938/1,223) patients thought the tablet was too big, 93.1% (1,139/1,223) patients thought the number of pills was too much in Shandong Province. 57.3% (647/1,130) patients thought the tablet was too big, 82.8% (936/1,130) patients thought the number of pills was too much in Jilin Province. 85.4% patients felt uncomfortable in the first 2-months of treatment, only 10.1% patients felt uncomfortable in the last 4-months of treatment in Shandong Province. 93.3% felt uncomfortable in the first 2-months of treatment, only 3.4% felt uncomfortable in the last 4-months of treatment in Jilin Province. Table 6 provides the results of treatment outcome for TB patients with and without compliance.

Drug substitution

The total replacement rate of loose drug replacing FDC was 2.0% (48/2,353). The replacement rate of Shandong Province and Jilin Province was 2.8% (34/1,223) and 1.2% (14/1,130), respectively. There was a significant difference in the replacement rate between two programs (χ^2=6.979,

Table 7 - Treatment outcome of standardized therapy for TB patients with and without drug substitution.

Substitution	*Province*	*N*	*Smear-positive**	*Cure N (%)*	*Effective n (%)*
No	Shandong	1188	378	364 (96.30)	1139 (95.88)
	Jilin	1110	369	341 (92.41)	1096 (98.74)
	χ^2	–	–	5.309	17.645
	p	–	–	0.021	<0.001
Yes	Shandong	34	6	6 (100.00)	33 (97.06)
	Jilin	14	4	4 (100.00)	13 (92.86)
	χ^2/Fisher	–	–	–	–
	p	–	–	–	0.503

*smear-positive means the number of smear-positive before the treatment in different groups.

p=0.008). Table 7 provides the results of treatment outcome for TB patients with and without drug substitution.

DISCUSSION

This study compared the efficacy and safety of two FDC regimens in two high TB-burden provinces, Jilin and Shandong. The findings of this study have important significance for medical practice in Chinese national TB program. There were five main findings:

1) The sputum negative conversion rate of Jilin Province at the end of intensive treatment was higher than that of Shandong Province;
2) The cure rate in Shandong Province was superior to Jilin Province. However, the treatment success rate of Shandong Province at the end of treatment was inferior to Jilin Province;
3) The incidence of adverse reactions in Shandong Province was lower than Jilin Province;
4) Both regimens showed similar patient compliance;
5) The replacement rate of loose drug replacing FDCs of Shandong Province was higher than that of Jilin Province.

The sputum negative conversion rates after 2-months of treatment for two provinces were similar to those in previous reports [10, 11]. A number of clinical studies demonstrated that a 6-months FDC regimen was found to be highly effective for patients with active pulmonary TB. Their treatment success rate ranges from 80% to 100%, which is consistent with our results [10-12]. Meanwhile, successful TB treatment outcomes in our study have reached the 85% threshold recommended by WHO [13, 14]. Although efficacy is a consideration, adverse reaction events are also an important factor influencing regimen selection. Some studies have shown that the incidence of ADRs and liver damage of FDCs is lower than separate formulations [11, 12]. The most frequent adverse reactions reported in both FDC regimens were digestive symptoms in our study. A retrospective cohort study performed by Mohammad et al. also found FDC group had higher incidence of gastric adverse events. Nevertheless, Wu et al. found the symptoms of skin disorders were the most common adverse reactions in FDC group [10, 15]. One possible reason for the difference is that our study population differs from other studies.

The difference between two regimens was the dosage of rifampicin and isoniazid in continuation phase treatment. Some studies reported that the bioavailability of rifampicin is an important factor in tablet [16, 17]. A meta-analysis comparing rifampicin and isoniazid with other treatment regimens showed shorter rifamycin-based regimens may have comparable benefits to longer isoniazid regimens for latent TB infection [18]. The dosage of rifampicin in Shandong Province is more than that in Jilin Province, which may be the reason that Shandong Province has a higher cure rate than Jilin Province. The patients from Shandong Province took drugs daily in the continuation phase and developed a habit. While the patients from Jilin Province took drugs every other day, it may be difficult to take drugs regularly, which leads to adverse reactions.

This study has certain limitations. Due to the restriction of inclusion and exclusion criteria, many

TB patients who may benefit from this study were not included in the study. Moreover, many elderly patients were included in the study, and their high rate of co-morbidities may have affected the incidence of adverse reactions and their ability to complete the follow-up.

In conclusion, the regimens of Shandong Province and Jilin Province have achieved good results, FDC regimens have been shown to be well tolerated and effective in patients with active pulmonary TB. The integral analysis showed both regimens had similar efficacy, but the regimen of Jilin Province was inferior to Shandong Province in terms of safety. Future research should be performed in large samples in order to provide a further scientific basis.

DATA AVAILABILITY

The datasets generated or analyzed during the current study are available from the corresponding author (Qiong Yu, email: yuqiong@jlu.edu.cn) upon a reasonable request.

Funding

This study was funded by special project of National thirteen Five Years Plan (2018ZX10722-301-004). The authors thank all cooperating organizations for their support.

Conflicts of interest

None declared.

Authors contrubution

Yaoyao Sun and Bonan Cao contributed equally to this article.

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