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Original Research Article

Therapeutic effect of cycloserine combined with anti-tuberculosis drugs in the treatment of multidrug-resistant tuberculosis

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Abstract

Purpose: *The present study analyzes the comprehensive therapeutic effect of cycloserine, in combination with anti-tuberculosis drugs using chest X-ray and chest CT (computed tomography) scan techniques.*
Methods: *A total of 90 patients, diagnosed with multidrug resistant tuberculosis (MDR TB) were subjected to chest x-ray and CT scan before and after treatment in the two groups. Different views such as sagittal, coronal, lung window and multiplanar imaging of mediastinal window were taken. Some parameters such as case detection rate (CDR) in chest X-ray and CT scan and comprehensive curative effect were observed in two groups. Further, the changes in chest CT signs in addition to absorption of focus, cavity closure and changes in CT extra pulmonary signs were also observed.*
Results: *The clinical profile of the patients and the course of disease were statistically insignificant ($p > 0.05$). Total effectiveness rate and case detection rate (CDR) values exhibited a significant difference between the groups ($p < 0.05$). Lung consolidation, nodules and cavities significantly improved in both groups before and after the treatment ($p < 0.05$). Both groups showed significant improvements in extrapulmonary signs in CT scan ($p < 0.05$) after the treatment.*
Conclusion: *Based on the study outcomes, the CT scan method has good potentials for diagnosing and treating MDR TB at the early stages. Further, it can clarify the signs and outcomes of the disease at early stages, thus providing the medical fraternity a great opportunity to cure the disease.*

Keywords: *CT scan, Cycloserine, Anti-tuberculosis treatment, Multidrug-resistant tuberculosis, Efficacy assessment*

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INTRODUCTION

Tuberculosis (TB), a chronic infectious disease, is caused by Mycobacterium tuberculosis among human beings which remained the main cause of death globally in the year, 2019 [1]. According to a research, an approximate of two billion people gets infected with Mycobacterium tuberculosis while 10 million new active tuberculosis patients are recorded with 1.7 million deaths every year [2]. Multidrug-resistant TB accounts for almost 25% of global TB death. This drug resistance

phenomenon refers to first-line resistance of Mycobacterium tuberculosis to isoniazid and rifampicin. China has high incidence of tuberculosis due to which the World Health Organization (WHO) listed it as one of the countries that suffer from high burden of MDR-TB. This in turn has serious effects on the health index of Chinese citizens [4,5]. At present, TB is mainly treated with chemotherapy. But the emergence of MDR-TB makes its treatment, a challenging process. Cycloserine is a second-line anti-tuberculosis drug whereas Mycobacterium tuberculosis exhibits low drug resistance against this second-line drug. At present, WHO has approved cycloserine to treat multi-drug resistant tuberculosis [6]. In clinics, X-ray chest film is often used to diagnose pulmonary tuberculosis. However, this technique could not be applied further to analyze the internal structure or observe the subtle changes brought by pulmonary tuberculosis. These disadvantages in X-ray chest film inhibit the diagnosis and treatment of pulmonary tuberculosis [7]. Computerized Tomography (CT) technique has various advantages such as high sensitivity, high accuracy, mitigation of overlapping, defining the nature of lesion and determination of size, scope and adhesion of lesion [8]. Therefore, this technique plays an important role in diagnosing TB and helps in further treatment. The current study is aimed at analyzing the effectiveness of CT in evaluating the clinical application of cycloserine, in combination with anti-tuberculosis drugs, in treating multi-drug resistant tuberculosis.

METHODS

Ethical statement

The authors ensured the accuracy and integrity of whole work and hold the complete responsibility for all the aspects of this investigation performed in this research study. All the methods mentioned in this work followed the guidelines in accordance with the "Declaration of Helsinki (as revised in 2013)" [10]. The study protocol was approved by institutional ethical board, Zhejiang Provincial Integrated Chinese and Western Medicine Hospital, Hangzhou, Zhejiang Province, China (NO.: 2019/MTB/01). Informed consent was taken from all individual participants before the study was initiated with the condition that the participant can withdraw from the study at any point of time.

Patient selection criteria

A total of 90 patients, diagnosed with MDR-TB and admitted at the study hospital between March 2018 and January 2020, was selected. The selected patients were randomly divided into two groups such as control group and study group with 45 cases in each group. Patients, who are aged 18 and above and confirmed to be positive for multi-drug resistant tuberculosis through M. tuberculosis smear diagnostic procedure in line with "Guidelines for Chemotherapy of Drug-Resistant Tuberculosis" [9], were selected for the study. Informed consent was obtained from the selected patients. The exclusion criteria for the study were patients who are allergic to the drug used in this study, who suffer from co-morbidities such as lung tumors, asthma, bronchopneumonia and other lung diseases, severe organic dysfunction specifically heart, lung, liver, kidneys and those who have communication disorders and mental illness.

Treatment regimen

The control group was provided with a routine set of anti-tuberculosis drugs. The dosage levels were as follows; 1.5 grams of pyrazinamide per day (approval No. gyzz h32024174, Jiangsu Sihuan Biopharmaceutical Co. Ltd), 1.5 grams of levofloxacin per day (approval No. gyzz h20083528, Biochemical Pharmaceutical Factory of Zhuhai Special Economic Zone), 1.5 grams of propylthioisoniazid per day (approval No. gyzz h31021180, Shanghai Shangyao Xinyi Pharmaceutical Co. Ltd.) and 24.5 mg of ethambutol per kg of body weight (approval No.: gyzz h31021140, Shanghai Xinyi Pharmaceutical Co. Ltd). For patients under study group, the treatment regimen was followed in line with the control group, whereas only cycloserine (approval no. h20140984, Dong-A st Co., Ltd.) was added in addition to the control group regimen. The dosage was adjusted according to the patient's condition and weight i.e., 0.5 to 1.0 grams per day. Along with the treatment regimens mentioned above, the patients in both groups were supplied with 150 mg/day vitamin B6 (approval No.: gyzz h31020308 manufacturer: Shanghai Xinyi Huanghe Pharmaceutical Co. Ltd.). The treatment was conducted for six months period.

Diagnostic procedures

Chest X-ray and CT scanning were performed, before and after the treatment, in both the groups to observe the lesions. Chest CT scan included different views such as sagittal, coronal, lung window and multiplanar imaging of mediastinal window. The results obtained from X-ray and CT scan were reviewed and reported by senior consultants of the Imaging Department. The

author(s) observed few parameters before and after treatment such as Case Detection Rate (CDR) in chest X-ray and CT scan, comprehensive curative effect in two groups and changes in chest CT signs in addition to absorption of focus and cavity closure and changes in CT extra pulmonary signs. The comprehensive therapeutic effect was divided into three subcategories based on its effectiveness such as significant, effective and ineffective. The first category i.e., Significant effect infers the thinning of cavity wall with reduction degree > 1 / 2 of the original cavity while the absorption of the focus > 1 / 2 of the original lesion; the second category denotes the thinning of cavity wall while the reduction degree is 1 / 3 ~ 1 / 2 of the original cavity and the absorption of the focus is 1 / 3 ~ 1 / 2 of original lesion; In the third category, there is new disseminated focus or a lack of change in invalid cavity and its focus.

Statistical analysis

The collected data was analyzed using SPSS (Ver. 19.0, SPSS Inc, IBM, USA) and the measurements are expressed as mean ± SD. The study used independent sample t-test. Count data is expressed as frequency (n) and percentage (%) using χ^2 test. $P < 0.05$ was considered statistically significant.

RESULTS

General conditions of the patients

As shown in table 1, age, sex, Body Mass Index (BMI) and course of disease of patients in control and study groups were not statistically significant (P > 0.05), but was comparable.

Therapeutic effect

Table 2 shows that the total effective rate of the control group (82.22 %) was effectively lesser than the study group (100%), and is statistically significant ($p < 0.05$).

Chest r-ray and CT reports

As shown in Table 3, the case detection rate of chest CT pulmonary tuberculosis before treatment in the two groups was significantly higher than that of x-ray, with a statistically significant difference ($p < 0.05$). Pulmonary consolidation, calcification, nodules, and cavitation are common signs of tuberculosis observed in CT [10-12]. The results indicate that the lung signs in study group got significantly reduced ($p < 0.05$) in comparison with control group as shown in Figure 1.

Table 1: General clinical profile of the patients such as age, gender, body mass index (BMI) and course of disease in control and study groups. The values seem to be statistically insignificant ($p > 0.05$)

Variable	Control group	Study group
Age (years)	44.29±4.27	43.24±4.65
Sex		
Male (n)	29 (64.4%)	30 (66.7%)
Female (n)	16 (35.6%)	15 (33.3%)
BMI（kg/m^2）	28.85±3.39	29.02±3.18
Duration of disease (years)	7.82±1.11	8.14±1.35

Table 2: Total effectiveness rate of control group (82.22 %) and study group (100 %). The values seem to be statistically significant ($p < 0.05$)

Group	Highly effective	Effective	Ineffective	Total effectiveness rate (%)
Control n (%)	15（33.33）	22（48.89）	8（17.78）	37（82.22）
Study n (%)	23（51.11）	22（48.89）	0（0.00）	45（100.00）$^{\#}$

$^{\#}P < 0.05$, compared with control group

Table 3: Chest x-ray and CT results – Pretreatment Case Detection Rate of chest CT in pulmonary tuberculosis was significantly higher than that of X-ray before treatment in two groups with statistically significant difference ($p < 0.05$)

Variable	Control group		Study group	
	Negative	***Positive***	***Negative***	***Positive***
X-ray, n (%)	5（11.11）	40（88.89）	7（15.56）	38（84.44）
CT, n (%)	0（00.00）	45（100.00）*	0（00.00）	45（100.00）*

Compared with x-ray, $^{*}p < 0.05$

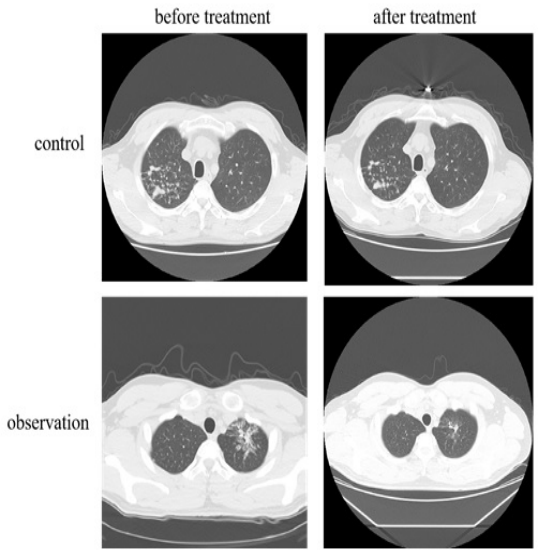

Figure 1: Computed tomography scan images of control and study subjects

Lung consolidation, nodules and cavities got significantly improved in both groups before and after the treatment ($p < 0.05$). When compared with control group, the study group showed significant improvements ($p < 0.05$) in lung consolidation, nodules and cavities. There was no significant difference in pulmonary calcification between the groups ($p > 0.05$), as shown in Table 4.

Lesion absorption and cavity closure after treatment

Both the groups were compared for lung lesion absorption and cavity closure after the treatment. As shown in Table 5, the total absorption rate of lesions and closure rate of cavities in the study group were found to be significantly higher than the control group, with statistically significant difference ($p < 0.05$).

Table 4: CT signs of lung between two groups before and after treatment

	Before treatment	
Variable	***Control group***	***Study group***
Consolidation n (%)	18（40.00）	15（33.33）
Calcification n (%)	9（20.00）	7（15.56）
Cavitary n (%)	22（48.89）	17（37.78）
Nodule n (%)	20（44.44）	21（46.67）
	After treatment	
Variable	***Control group***	***Study group***
Consolidation n (%)	11（24.44）*	3（6.67）*#
Calcification n (%)	11（24.44）	10（22.22）
Cavitary n (%)	7（15.56）*	1（2.22）*#
Nodule n (%)	9（20.00）*	2（4.44）*#

*$P < 0.05$ compared with pre-treatment, #p＜0.05 compared with control group

Extra pulmonary signs in chest CT before and after treatment

As shown in Table 6, there was no significant difference in mediastinal lymph node enlargement and pleural effusion between the groups before treatment ($p > 0.05$). However, the control group and the study group showed significant improvements in extrapulmonary signs in CT scan ($p < 0.05$) after the treatment. When compared with control group, the study group got improved significantly ($p < 0.05$).

Table 5: Lung lesion absorption and cavity closure after treatment

Variable	Parameter	Control study n (%)	Study group n (%)
Lesions absorption	Obvious absorption	19（42.22）	28（62.22）#
	Absorption	14（31.11）	14（31.11）
	No absorption	12（26.67）	3（6.67）#
	Total absorption rate	33（73.33）	42（93.33）#
Cavity closure	Total closure	15（33.33）	22（48.89）#
	Reduction 1/2	15（33.33）	20（44.44）
	Reduction 1/3	7（15.56）	3（6.67）
	No reduction	8（17.78）	0（0.00）#

Compared with control group, #$p < 0.05$

Table 6: Extrapulmonary complications before and after treatment

	Control group n (%)		Study group n (%)	
Variable	***Before treatment***	***After treatment***	***Before treatment***	***After treatment***
Mediastinal lymphadenopathy	18（40.00）	11（24.44）*	22（48.89）	4（8.89*#
Pleural effusion	14（31.11）	7（15.56）*	10（22.22）	1（2.22）*#

*$P < 0.05$ compared with pre-treatment; #$p < 0.05$ compared with control group

DISCUSSION

Tuberculosis remains a major health burden for countries across the globe in spite of huge investments made in research and development, treatment and preventive strategies designed to curb the disease. At present, a combination of rifampicin and isoniazid is an important drug regimen to treat tuberculosis. However, the unreasonable drug usage in the past led to the emergence of drug-resistant tuberculosis bacteria and multi-drug-resistant bacteria. This scenario poses serious challenges to the established TB treatment regimens [3]. According to the literature [4], the cure rate of MDR-TB is 50% [4]. When Mycobacterium tuberculosis is resistant to first-line anti-tuberculosis drugs such as rifampicin and isoniazid, it can be treated with second-line drugs, which have better efficacy and less toxicity [5]. Cycloserine, a cyclic analogue of D-alanine, was discovered in 1954 as a second-generation anti-tuberculosis drug [6]. Cycloserine competitively inhibits alanine racemase and D-alanine–D-alanine ligase which are required for cell wall synthesis of Mycobacterium tuberculosis, thereby exerting anti-tuberculosis effects [7,8]. The current study found that when patients, diagnosed with pulmonary tuberculosis, underwent cycloserine intervention, they showed improvements in lung consolidation, nodules and cavities compared with the control group. Further, pulmonary lesion absorption and cavity closure got significantly improved compared to the control group. This infers that cycloserine, in combination with anti-tuberculosis drugs, can treat pulmonary tuberculosis in an effective manner. At present, tuberculosis is clinically diagnosed based on patient's symptoms, positive sputum culture and imaging methods [9]. Positive sputum culture is the gold standard for clinical diagnosis. However due to technological limitations, the positive rate of sputum examination is not high. This results in late diagnosis of sputum-negative tuberculosis (PTB) and extrapulmonary tuberculosis (EPTB). So, imaging-based diagnosis can be used as a common diagnostic method for TB in patients [10,11]. On the contrary, few symptoms of tuberculosis may resemble tumor or sarcoidosis which question the accuracy of diagnostic procedure results. Early diagnosis of tuberculosis not only paves the way for an effective treatment, it can also reduce the further spread of tuberculosis [12]. X-ray and CT scan are common imaging methods in the diagnosis of pulmonary tuberculosis [13,14]. X-ray is often unclear for small concealed pulmonary lesions and hilar and mediastinal lymph nodes. This might result in undetected proliferation of the disease in some patients [15]. Normal or non-specific manifestations can be observed on chest x-ray at some times in patients with active pulmonary tuberculosis [16]. When compared with x-ray, CT scan method has no structural overlap, captures images with high resolution and better in the detection of solid disease, mediastinal lymph node enlargement and pleural disease, which can evaluate the subtle characteristics of lesions [17,18]. It is easy to find occult, thoracic, tracheal and bronchial lesions. Further, the method helps in identifying the cavities, deterioration and improvement of absorption [18]. The current study found that the CDR of chest CT in pulmonary tuberculosis was significantly higher than that of the X-rays in both groups before treatment. The changes in chest CT signs of those patients, before and after getting treatment with conventional anti-tuberculosis drug regimen and cycloserine, were compared. The results inferred that pulmonary CT signs could clearly show lung consolidation, nodules and cavities.

Limitations of the study

The clinical complications and symptoms of TB vary from one stage to another. The current study is limited to MDR-TB and did not consider its different stages. The future studies are suggested to explore the efficacy of CT scan and cycloserine in diagnosing and treatment of other stages of TB and present their implications.

CONCLUSION

Computed tomography scan method can help in the diagnosis and treatment of multidrug-resistant pulmonary tuberculosis since it has the capacity to clarify signs and prognosis of the disease. Thus, the method adds significant value to the diagnostic procedures and clinical treatment of MDR-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. Yang Zhao and Mabin Si - Literature search, Data analysis, Statistical analysis, Manuscript preparation,

Manuscript review, Guarantor. Yang Zhao, Zhihui Li and Xiulei Yu- Concepts, Design, Definition of intellectual content, Literature search, Experimental studies, Data acquisition, manuscript editing.

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