Efficacy and Safety of Bronchoscopic Cryotherapy for Granular Endobronchial Tuberculosis

Deguang Mu Dongyan Nan Wangping Li Enqing Fu Yonghong Xie
Tonggang Liu Faguang Jin

Department of Respiratory Disease, Tangdu Hospital, Fourth Military Medical University, Xi'an, China

Key Words

Bronchial stenosis • Cryotherapy, bronchoscopic •
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Abstract

Background: The most important sequela of endobronchial tuberculosis (EBTB) is bronchial stenosis, which causes wheezing, dyspnea and obstructive pneumonia. But there have been no reports about applying cryotherapy for granular EBTB that did not show luminal narrowing of the bronchus at diagnosis. Whether this technique is useful for preventing granular EBTB from progressing into stenosis needs to be clarified. **Objective:** To investigate the efficacy and safety of bronchoscopic cryotherapy for granular endobronchial tuberculosis. **Methods:** In this study, we analyzed the records of 76 patients with granular EBTB. Diagnosis of TB was confirmed by microbiology or histopathology. Bronchoscopic examinations revealed that the patients had granular endobronchial tuberculosis. Thirty-eight patients received bronchoscopic cryotherapy plus routine anti-tuberculosis chemotherapy and the other 38 patients received routine anti-tuberculosis chemotherapy alone. We compared the treatment effect of these 2 groups. The outcome measures were the changes of lesions, the rate of disappearance of le-

sions and complications of bronchoscopic cryotherapy. **Results:** The complete removal rate was 100% in patients with bronchoscopic cryotherapy plus routine anti-tuberculosis chemotherapy; the complete removal rate was 78.9% in patients with anti-tuberculosis chemotherapy alone; the rate of disappearance of lesions in the bronchoscopic cryotherapy plus routine anti-tuberculosis chemotherapy group was faster than that of the anti-tuberculosis chemotherapy alone group. There were no severe complications from bronchoscopic cryotherapy. **Conclusions:** Bronchoscopic cryotherapy can accelerate the healing of granular EBTB and help to prevent progressive bronchial stenosis due to granular EBTB and is a very safe method.

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Introduction

Endobronchial tuberculosis (EBTB) is defined as a tuberculous infection of the tracheobronchial tree with microbial and histopathological evidence. EBTB is divided into 7 types according to bronchoscopic features: actively

D.M. and D.N. contributed equally to this paper.

Fig. 1. Bronchoscopic features and treatment result of granular EBTB. **a** Bronchoscopic features of granular EBTB. **b** Treatment of the lesion. **c** Treatment result.

caseating; edematous-hyperemic; fibrostenotic; tumorous; granular; ulcerative, and nonspecific bronchitic [1]. A proportion of granular EBTB changes into the fibrostenotic type [1, 2].

The most important sequela of EBTB is bronchial stenosis, which causes wheezing, dyspnea and obstructive pneumonia. Various bronchoscopic techniques applied to treat stenotic lesions include laser [3] and cryosurgery [4] through a fiberoptic bronchoscope. There have been no reports about applying cryotherapy for granular EBTB that did not show luminal narrowing of the bronchus at diagnosis. Whether this technique is useful for preventing granular EBTB from progressing into stenosis needs to be clarified.

Here we analyzed the treatment effect in 76 patients with tracheobronchial tuberculosis in our hospital to determine the efficacy and safety of bronchoscopic cryotherapy for granular EBTB.

Methods

Study Subjects

We analyzed the records of patients who were diagnosed with and treated for granular EBTB in our department from February 2004 through January 2009. Seventy-six patients were eligible for enrolment of our study.

The study was approved by the medical ethics committee of the Fourth Military Medical University. The diagnostic criteria of granular EBTB and categories for patient selection were as follows: (1) Diagnosis of tuberculosis was confirmed by microbiology or histopathological examination. All patients underwent bacteriologic studies of sputum and bronchoscopic aspirates, and they also underwent pathologic studies of bronchoscopic biopsy specimens.

(2) Granular EBTB was defined according to Hee Soon Chung's report as shown in figure 1.

The exclusion criteria used in this study were:

- (1) History of previous anti-tuberculosis therapy.
- (2) Having another subtype of EBTB or already having bronchial stenosis.

Treatment Procedure

Bronchoscopic cryotherapy was performed with a flexible bronchoscope with a working channel of 2.8 mm (BF-260; Olympus) using the flexible cryoprobe. The cryoprobe had an operating diameter of 2.4 mm, length of 90 cm, and the length of the tip is 7 mm (ERBE USA Inc.). Carbon dioxide was used as the cryogen. The freeze-thaw cycles were of 1 min duration. Bronchoscopic cryotherapy was performed every 2 weeks. If there were no granular bronchial tuberculosis lesions, the bronchoscopic cryotherapy was terminated.

Routine anti-tuberculosis chemotherapy was the conventional combination of isoniazid, rifampicin, ethambutol and pyrazinamide for 2 months followed by isoniazid and rifampicin for 4 months.

Bronchoscopic Examination and Follow-Up

The patients received bronchoscopic examination every 2 weeks from the beginning of the treatment for 6 months. Then 6 months later, the patients received bronchoscopic examination once every month for 3 months.

Outcome Events

The outcome measures were change in lesions and rate of lesion disappearance. The secondary outcome was complications of bronchoscopic cryotherapy. Change in lesions was categorized into 4 groups:

- improved: the number and/or volume of granular lesions was reduced;
- healed: the lesions were completely removed;
- stationary: no change in the number and/or volume of lesions;
- worsened: the volume and/or number of lesions increased.

Results

Before June 2007, we applied only routine anti-tuberculosis chemotherapy alone for granular EBTB and several cases developed into bronchial stenosis. By using bronchoscopic cryotherapy we resolved the stenosis. After June 2007, we began applying cryotherapy for granular EBTB patients. Between February 2004 and January 2009, 407 patients were diagnosed with granular EBTB and 191 met the requirements of the inclusion but not the

exclusion criteria. Among these 191 patients, 71 received bronchoscopic cryotherapy plus routine anti-tuberculosis chemotherapy and 120 received routine anti-tuberculosis chemotherapy alone. Among the 71 with chemotherapy plus cryotherapy and 120 with only chemotherapy, 62 and 105 patients completed the bronchoscopic examination and follow-up, respectively. Complete recovery was seen in all 62 patients in the chemotherapy plus cryotherapy group and in 89 of the 105 patients in the chemotherapy alone group. The lesions of the other 16 patients in the chemotherapy alone group were stationary or worsened. We applied cryotherapy to them and those patients were finally completely cured.

We selected 38 patients of each group into our study based on the comparability of their characteristics (such as age, severity of their lesions, sex, bronchoscopic features) before treatment. No dyspnea or obstructive pneumonia presented at the beginning of the treatment. The main symptoms were fever, irritant cough, chest pain. Table 1 summarizes the baseline characteristics of the study population. Figure 1 shows the features of granular EBTB, treatment with bronchoscopic cryotherapy and treatment results.

Localization of Lesions

There were 263 lesions found in the 76 patients. The localization and number of lesions were as follows: trachea 8 (3%); left main bronchus 67 (25.5%); left upper lobar bronchus 55 (20.9%); left lingual lobar bronchus 25 (9.5%); left lower lobar bronchus 22 (8.4%); right main bronchus 12 (4.6%); right upper lobar bronchus 28 (10.6%); right middle lobar bronchus 21 (8%); right lower lobar bronchus 25 (9.5%) (table 1).

Change of Lesions in the Cryotherapy plus Chemotherapy Group

Patients received cryotherapy a mean of 4 times, and all patients were completely healed. The duration from the start of the therapy to complete lesion disappearance was about 2 months. No stenosis appeared due to EBTB (table 2).

Among those 38 patients in the conventional chemotherapy group, 29 were completely healed, and the duration from the start of the therapy to complete disappearance of the lesions was about 5 months. The lesions in 6 patients showed no change after 4 months of treatment. The lesions in 3 patients were aggravated. In order to remove the lesions in these 9 patients, we applied bronchoscopic cryotherapy to remove these lesions and they were finally completely healed (table 2, 3).

Table 1. Clinical characteristics of the 76 patients

	Bronchoscopic cryotherapy plus anti-tuberculosis chemotherapy	Anti-tuberculosis chemotherapy alone
Mean age $\pm$ SD, years	34.5 $\pm$ 12.6	32.5 $\pm$ 11.1
Female	25	22
Diagnosis of pulmonary tuberculosis		
AFB smear only	4	3
Histopathology	26	27
Location of airway lesions		
Trachea	5	3
Right main bronchus	6	6
Right upper lobar bronchus	13	15
Right middle lobar bronchus	8	13
Right lower lobar bronchus	13	12
Left main bronchus	39	28
Left upper lobar bronchus	25	30
Left lingual lobar bronchus	10	15
Left lower bronchus	14	8

There were no severe complications from bronchoscopic cryotherapy. The only complication from bronchoscopic cryotherapy was bleeding. Bleeding occurred 15 times during the treatment due to cryotherapy and the amount of blood was less than 20 ml. By locally spraying 1:10,000 adrenaline we successfully stopped the bleeding.

Discussion

Tracheobronchial tuberculosis is a kind of tuberculous inflammation that occurs at the trachea or bronchial mucosa. EBTB has been reported in 10–37% of patients with pulmonary tuberculosis and more than 90% of patients with tracheobronchial tuberculosis have some degree of bronchial stenosis [5–7]. In recent years, the incidence of pulmonary tuberculosis has increased in China [8] which results in an increasing incidence of tracheobronchial tuberculosis. Pathologically, the initial lesion presents as simple erythema and edema of the mucosa. This lesion is followed by submucosal tubercle formation. When the inflammation erupts through mucosa, an ulcer is seen that may be covered by caseous material. Finally, the bronchial mucosal ulcer evolves into hyperplastic inflammatory polyps, and the tracheobronchial tuberculous lesion heals by fibrostenosis [9] which results in the bronchial obstruction and various complications such as stelectasis and obstructive pneumonia. Thus, it is impor-

Table 2. Bronchoscopic findings of the 38 cases in the cryotherapy plus chemotherapy group and the 29 cases in the chemotherapy alone group

Time point	Cryotherapy + chemotherapy (number of cases)				Chemotherapy alone (number of cases)			
	healed	improved	stationary	worsened	healed	improved	stationary	worsened
2 weeks	2	36	0	0	0	28	1	0
4 weeks	6	32	0	0	0	28	1	0
6 weeks	20	18	0	0	0	29	0	0
8 weeks	24	14	0	0	1	28	0	0
10 weeks	35	3	0	0	5	24	0	0
12 weeks	36	2	0	0	10	19	0	0
14 weeks	38	0	0	0	19	10	0	0
16 weeks					22	7	0	0
18 weeks					27	2	0	0
20 weeks					29	0	0	0

Table 3. Medical regimen and bronchoscopic findings of the 9 cases with cryotherapy intervention in the anti-tuberculosis chemotherapy group

Case	Age	Sex	Change of lesions							
1	52	M	4	4	4 ↓	1		1	2	
2	43	M	3	3	3 ↓	1		2		
3	55	M	4	4	4 ↓	1		1	2	
4	61	F	4	4 ↓	1	1		2		
5	46	F	3	3	3 ↓	1		1	2	
6	45	M	3	3	3 ↓	1		2		
7	38	F	3	3	3 ↓	1		1	2	
8	27	M	3	3	3 ↓	1		2		
9	42	M	3	3	3 ↓	1		2		

Bronchoscopic findings: 1 = improved; 2 = healed; 3 = stationary; 4 = worsened. ↓ = Bronchoscopic cryotherapy was started.

tant to prevent bronchial stenosis and complications in patients with EBTB.

Hoheisel et al. [10] described that tracheobronchial stenosis may develop in spite of adequate anti-tuberculosis therapy. Our results with conventional therapy were similar to this study. Figure 1 is representative of a large portion of the 76 cases, although in some instances the lesions were smaller than the one shown. Those smaller lesions can be cured using anti-tuberculosis alone, but the duration of the treatment was longer than those treated

by cryotherapy plus anti-tuberculosis, as shown in table 2. Before 2007, we use only anti-tuberculosis alone for granular EBTB. Even with lesions smaller than the one shown in figure 1, some patients worsened and progressed to bronchial stenosis. This situation caused us to apply cryotherapy plus anti-tuberculosis chemotherapy for granular EBTB from 2007.

In our study, among the anti-tuberculosis chemotherapy group, about 6 patients had no improvement even after therapy for 4 months. The condition of 3 patients even became aggravated and resulted in bronchial stenosis and obstruction of the lumen. We applied cryotherapy to treat these 9 patients. After about 3 rounds of therapy, the lesions were finally removed and the patients were healed.

With the development of interventional bronchoscopic techniques, many new methods such as laser, APC and stent are used to treat the bronchial stenosis due to EBTB [11]. But there were no reports about the use of cryotherapy for granular EBTB which did not obstruct the trachea or bronchus to prevent further stenosis.

In this study, we analyzed the treatment effect in 76 patients with granular EBTB in our hospital. As the results show, bronchoscopic cryotherapy can accelerate the healing of granular lesions. Conventional chemotherapy cannot completely prevent the lesions from progressing into stenosis.

Um et al. [12] reported that age >45 years was identified as an independent predictor of persistent bronchostenosis. Consistent with their result, in our study, the mean age of those patients whose lesions changed into stenosis was 45.4 years. So when a patient had granular

EBTB and was older than 45 years, in addition to anti-tuberculosis chemotherapy, bronchoscopic cryotherapy was recommended for preventing lesion progression to stenosis.

Recently, there has been a trend towards increased complications from bronchoscopy [13] but there were no

severe complications during the cryotherapy treatments. The only complication from bronchoscopic cryotherapy was minor bleeding. So the cryotherapy was an effective and safe method for the management of granular EBTB.

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