BMC Surgery

RESEARCH

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Application value of fibro-bronchoscopic cryosurgery combined with medication in the treatment of tracheobronchial tuberculosis

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Abstract

Objective To investigate the value of fibro-bronchoscopic cryosurgery combined with medication in the treatment of tracheobronchial tuberculosis (TBTB).

Methods This study was designed as a prospective, randomized clinical trial. 96 patients with newly diagnosed TBTB were collected and divided into the study group ($n=48$) and the control group ($n=48$). Specifically, conventional anti-tuberculosis therapy was given to the control group, with the study group undergoing fibro-bronchoscopic cryosurgery combined with topical administration. Afterward, the post-treatment response rate and adverse reaction indicators were collected for comparison.

Results After treatment for 6 months, the study group was superior to the control group in terms of clinical efficacy ($P=0.013$), negative conversion rate of acid-fast bacilli ($P=0.014$), and lesion recovery ($P=0.003$); after treatment for 6 months, the study and control groups exhibited no significant differences in the response rate of inflammatory infiltration ($P=1.000$) and granulation proliferation ($P=0.061$). Additionally, the study group showed a higher response rate of ulcer necrosis ($P=0.041$) and cicatricial stenosis ($P=0.029$) than the control group, with no significant differences observed in the incidence of adverse reactions between the 2 groups ($P=0.584$). Moreover, the clinical efficacy in the study group was higher than that in the control group after treatment for 12 months ($P<0.001$).

Conclusion The application of fibro-bronchoscopic cryosurgery combined with topical administration on the basis of conventional anti-TB treatment can improve the clinical efficacy of TBTB patients and shorten the duration of treatment without increasing the incidence of adverse reactions.

Keywords Tracheal tuberculosis, Bronchial combination, Fibro-bronchoscopy, Drug therapy, Cryosurgery

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Introduction

Tuberculosis (TB) is a systemic disease caused by Mycobacterium Tuberculosis (MTB), primarily transmitted through the air as a chronic infectious respiratory disease, while the lungs are the most commonly affected organs in TB infections, usually leading to severe cough, fever, and chest pain [1]. Pulmonary tuberculous cavities are the most common imaging findings of active TB, where MTB can proliferate extensively within the cavitary lesions, with a high bacterial load and strong activity in the necrotic debris. Since pulmonary tuberculous cavities are often in an active stage, the necrotic contents are continuously excreted from the bronchi, thus significantly increasing the risk of concurrent tracheobronchial tuberculosis (TBTB) [2, 3].

Tracheobronchial tuberculosis (TBTB), a special clinical type of tuberculosis, refers to tuberculosis that occurs in the mucosa, submucosa, smooth muscle, cartilage, and adventitia of the trachea and bronchi. TBTB is classified into 6 types: inflammatory infiltration (Type I), ulcerative necrosis (Type II), granulation proliferation (Type III), cicatricial stenosis (Type IV), tracheobronchial wall softening (Type V), and lymph node fistula (Type VI) [4, 5]. In addition to causing the same consumptive symptoms as tuberculosis, TBTB may lead to varying degrees of stenosis, obstruction, or even complete occlusion of the airways, including the central large airways (trachea, LMB, RMB, and right intermediate bronchus), resulting in varying degrees of dyspnea, difficulty in sputum clearance, recurrent infections, atelectasis, lung damage, and even asphyxia and death, which is a disease with high morbidity and mortality. It has been shown that 60–70% of TBTB patients are positive for sputum tuberculosis [6, 7], making TBTB a highly contagious disease that can easily lead to the spread of tuberculosis. Research has indicated that about 10–40% of active pulmonary tuberculosis is associated with TBTB [8]. According to a report released by WHO in 2019, there were 10 million new cases of pulmonary tuberculosis worldwide in 2018 [9], with 1.5 million deaths, equivalent to about 150,000 to 600,000 deaths from TBTB each year.

Despite being the fundamental treatment, standardized systemic anti-tuberculosis drug chemotherapies have minimal effects on TBTB with cicatricial stenoses and tracheobronchial wall softening [10]. Common surgical procedures include lobectomy, sleeve resection, and bronchoplasty, which can quickly relieve airway stenosis, mitigate complications, and reduce the risk of tuberculosis dissemination. However, these surgeries are highly invasive, with numerous complications and high costs [11]. In recent years, minimally invasive bronchoscopic interventional therapies have developed rapidly, showing significant efficacy in TBTB and reducing the occurrence of complications and sequelae, becoming an effective adjunctive therapy for TBTB [12]. Currently, the commonly used bronchoscopic interventional techniques for treating TBTB include microscopic topical administration, cryotherapy, thermal ablation, balloon angioplasty, and stent implantation [13]. Zhang Dong et al. [14] have actively explored the treatment of TBTB using techniques such as local drug injection, balloon dilation, argon plasma coagulation, or stent implantation, with results indicating significant efficacy. FRANKE et al. [15] applied cryosection (enucleation) techniques to treat airway obstruction caused by various reasons. However, to date, no single technique can comprehensively and thoroughly address the treatment issues of the diverse pathological types of TBTB, and many significant challenges remain [16], requiring continuous in-depth exploration.

Therefore, inspired by the above research, this study explored the clinical effect of the "fibro-bronchoscopy cryotherapy + cryosurgery + topical administration" technique for treating TBTB, thereby providing novel approaches and ideas for the precise treatment of TBTB.

Study subjects and methods

Study subjects

This study was a prospective, randomized clinical trial. 134 patients with newly diagnosed TBTB who were admitted to the Department of Tuberculosis in our hospital from June 2023 to August 2024 were collected through convenience sampling. All patients met the diagnostic criteria for TBTB and underwent fibro-bronchoscopy, and the results showed that tracheobronchial tuberculosis changes were clearly present in all patients and confirmed bacteriologically and/or pathologically. Following the inclusion and exclusion criteria, 96 patients with complete data were finally selected as the study subjects and randomly divided into the study group ($n = 48$) and the control group ($n = 48$). Patients were assigned to the study group and the control group based on randomized allocation. The randomization was performed using a computer-generated random number sequence to ensure unbiased distribution. The study group received the combined treatment of bronchoscopic cryotherapy and topical anti-TB management, while the control group received conventional anti-TB treatment alone. Patients were matched for age, gender, and disease severity to ensure comparability between the two groups. Ethical approval for this study was obtained from the ethics committee of Wenzhou Central Hospital (Approval No. WZXYLS-2023-Y-033). The ethical review ensured that all procedures followed international ethical standards, including patient consent and safety protocols. The use of topical treatment via injection of isoniazid, amikacin, levofloxacin, and dexamethasone into the local lesion site was approved as part of the study's innovative approach

to treatment, and all patients signed informed consent forms.

TBTB was diagnosed and classified following the criteria in the Guidelines for the Diagnosis and Treatment of Tracheobronchial Tuberculosis (Trial) [4]: Diagnosis: ① Typical TBTB lesions under bronchoscopy; ②Sputum smear positive for acid-fast bacilli or Mycobacterium tuberculosis culture positive; ③ Brush and lavage fluid positive for acid-fast bacilli; ④ Microscopic biopsy suggestive of tuberculosis pathological changes; patients diagnosed with TBTB who met ①+② or ①+③or ①+④. Highly suspected TBTB patients were those with typical TBTB lesions under bronchoscopy, combined with clinical manifestations, clinical treatment response, imaging changes, and positive for PPD tests. After the initial diagnosis of MTB, MDR (Multidrug-resistant tuberculosis) testing was performed on all patients using standard laboratory methods, including culture and drug susceptibility testing. The results of the MDR testing were considered when determining the treatment regimen for each patient. Only patients who were susceptible to first-line anti-TB medications were included in the study.

Classification: ① Type I (inflammatory infiltration): Lesions are primarily congestion and edema; ② Type II (ulcer necrosis): Lesions are mainly local ulcer and necrosis; ③ Type III (granulation proliferation): Lesions are predominantly local granulation tissue hyperplasia; ④ Type IV (cicatricial stenosis): Lesions are mainly scar formation, luminal stenosis or occlusion; ④ Type V (tracheobronchial wall softening): The affected tracheal and bronchial cartilage rings are absent or broken due to destruction, and the tracheal and bronchial lumens collapse due to the loss of supporting structure, leading to varying degrees of obstruction, especially evident when the expiratory phase and intrathoracic pressure increase, and the distal bronchi of the lesions may exhibit varying degrees of bronchiectasis; ③ Type VI (lymph node fistula): Broncholymphatic fistulas are caused by tuberculosis of mediastinal or hilar lymph nodes rupturing into the airways.

Inclusion criteria: (1) Patients who met the diagnostic criteria; (2) Aged 18–65 years; (3) Patients without serious heart, liver, and kidney disease who could complete the course of treatment as required; (4) Patients with good compliance who could actively cooperate with the treatment and undergo reexaminations for relevant items; (5) Patient who accepted regular outpatient follow-up and with complete medical records. Exclusion criteria: (1) Age < 18 years or > 65 years; (2) Patients with severe heart, liver, and kidney disease who couldn't tolerate anti-tuberculosis treatment; (3) Patients who suffered serious adverse drug reactions during treatment, leading to discontinuing anti-tuberculosis treatment for over 1 month, or changing the anti-tuberculosis treatment regimen; (4) Patients who self-terminated the treatment without reason, failing to undergo regular reexaminations as required, or lost outpatient follow-up, resulting in incomplete medical records.

Study methods

Standardized anti-tuberculosis treatment

Patients in the 2 groups were given standardized anti-TB treatment (Protocol 3HRZE/9HR), symptomatic treatment of relieving cough and reducing sputum for 12 months. Anti-TB treatment: Oral isoniazid (INH) 0.3 g once daily, rifampicin (RFP) 0.45 g once daily, ethambutol (EMB) 0.75 g once daily, and pyrazinamide (PZA) 0.5 g 3 times daily. Patients in both groups were treated with aerosol inhalation of isoniazid 0.1 g, twice daily for 10–15 min while undergoing systemic chemotherapy during hospitalization for more than 1 month.

The dosage of topical medications was calculated based on the patient's lesion area and body weight. First, the lesion area was determined using imaging examination. The required dosage of the medication was then calculated using the following formula:

Medication Dose (in mg) = Lesion Area (cm^2) × Dose per cm^2 (mg/cm^2).

The standard dose per cm^2 is referenced from XX (specific literature citation).

The topical medication was administered via a metered-dose spray. The medication was evenly sprayed onto the lesion area, with each treatment session lasting approximately 10 min. The treatment frequency was three times per week for a duration of four weeks.

Fibro-bronchoscopy

BF-1TQ170 electronic bronchoscope was used in the study (Olympus and Pentax, Japan), with a working channel diameter of 2.8 mm. All 96 patients underwent fibrobronchoscopy before treatment, aiming to observe the location, scope, and nature of airway lesions and to take specimens for bronchial smear or pathological examination, so as to confirm the diagnosis. Afterward, fibrobronchoscopy was performed again in all 96 patients after 6 months of treatment, with the aim of observing the recovery of airway lesions. Specifically, 48 patients in the study group agreed to receive fibro-bronchoscopic cryotherapy combined with injection therapy, and the treatment was given during hospitalization and once a week during the intensive phase of anti-tuberculosis treatment, ranging from 2 to 8 times according to the severity of the disease and the recovery of airway lesions observed during treatment.

Fibro-bronchoscopic interventional therapy

In the study group, fibro-bronchoscopic interventions were performed on the basis of the therapy given to the

control group, including cryotherapy and topical administration. CA multifunctional cryotherapy instrument was utilized for cryotherapy (Albos, Germany) using CO2 as the cold source and a flexible cryotip with a diameter of 2.4 mm and a total length of 780 mm.

Patient preparation: (1) CT and fibro-bronchoscopy were conducted to identify the location of the lesion, the degree of bronchial lumen blockage, and the extent of the lesion; (2) Systemic anti-TB chemotherapy was performed > 2 weeks; (3) ECG, coagulation function tests, and blood gas analysis of the patients were conducted before cryosurgery to identify no contraindications to fibro-bronchoscopy; (4) Fasting > 12 h, with heart rate, blood pressure, and oxygen saturation tested before cryosurgery; (5) All procedures were performed under local anesthesia with 2% lidocaine applied to the glottis and bronchial mucosa to minimize discomfort and suppress cough reflex. In cases where patients had severe airway stenosis or exhibited high procedural risk, a laryngeal mask airway (LMA) or endotracheal intubation was considered for better airway control and procedural safety. However, in most cases, no artificial airway was required, and spontaneous breathing was maintained throughout the procedure.

Cryosurgery: (1) Freeze-thaw process. Patients were placed in a supine position with their heads tilted back. Under low-flow oxygen inhalation, fibro-bronchoscopy was inserted through the nose, and the glottis and carina were topically anesthetized with 5–20 mL of 2% lidocaine, respectively, followed by reaching the site of bronchial tuberculosis lesions through fibro-bronchoscopy. Afterward, the flexible cryotip from the operation hole of the fibro-bronchoscopy was placed on the lesion before releasing and carefully inserting about 0.5 cm at the base of bronchial tuberculosis lesions, followed by pressing the cryoswitch to fix the cryotip. It could be seen that the lesion near the cryotip gradually cooled and formed into a hockey ball that turned white, and the diameter of the hockey ball was about 0.5–0.6 cm after 15–30 s, with the local temperature reduced to -50- -70℃. The pedal was released, and the cryotip was slowly thawed and returned to room temperature, and the cryotip and tissues were detached after thawing. Notably, the freeze-thaw process was performed repeatedly at different sites of the lesion to observe the bleeding of the lesion. Generally, the blood supply to the lesion site was significantly reduced after performing the freeze-thaw process 3–5 times; (2) Cryoresection. The direction and position of fibro-bronchoscopy were adjusted to allow the cryotip to attach to the lesion tissue from the surface before pressing the pedal to make the cryotip closely frozen together with the lesion tissue. Afterward, the cryotip was slowly pulled out to tear away part of the lesion tissue adhered to it, followed by releasing the pedal to allow the tissue to detach from the cryotip after the cryotip returned to room temperature. Meanwhile, the angle and depth of the cryotip contacting the lesion were adjusted, followed by repeated operation of cryosection, in which the cryotip should not be inserted too deep into the tissue (generally < 0.5 cm) with freezing for 5–8 s before detaching from the tissue (freezing too long led to an ice ball with a too large diameter, potentially damaging the airway wall mucosa). Through multiple resections of small tissues, the lesions obstructing the airway were removed piece by piece, achieving the objective of removing the lesion tissue and clearing the airway. Once resected, the small lesions were aspirated through the bronchoscope after rinse. For large lesion tissue mass, it is suggested to withdraw the fibro-bronchoscopy first and then re-insert it to observe whether there were bleeding or other issues at the resected site.

Topical administration: After cryotherapy, 0.2 g isoniazid (2 ml: 0.1 g), and 0.15 g rifampicin were injected into the local lesion site.

If patients experienced symptoms such as dyspnea, cyanosis, and asphyxia during the treatment, the operation should be immediately stopped, and the fibro-bronchoscopy should be withdrawn for observation, along with symptomatic treatment provided. The bronchoscopy room was equipped with first-aid equipment and emergency drugs.

This treatment course was performed once a week for 3 consecutive weeks as a course of treatment. Patients were treated for 1 to 3 courses according to their specific conditions.

Outcome indicators

The incidence of TBTB patients, including gender ratio, age of onset, and site of bronchial lesions.

Clinical manifestations and relief of symptoms after treatment in TBTB patients.

Changes in blood routine indicators, urine routine indicators, liver function, renal function, sputum acid-fast bacilli smear, and chest imaging during treatment in TBTB patients.

The type of microscopic lesions in TBTB patients, and the recovery from bronchial lesions observed through reexaminations via fibro-bronchoscopy after 6 months of treatment, including the absorption of bronchial mucosa, lumen, caseous necrosis, and granulomas.

Whether TBTB patients experienced adverse reactions to anti-TB drugs during treatment, as well as complications of fibro-bronchoscopy treatment.

Whether TBTB patients were clinically cured if they met discontinuation indicators after 12 months of treatment.

Efficacy determination

Determination of clinical efficacy

The efficacy date after 6 months of treatment was collected following the criteria from relevant literature [17]: Significantly effective: symptoms disappeared, sputum acid-fast bacilli smear turned negative, imaging showed lung lesions absorbed more than 1/2, bronchoscopy showed caseous necrosis or granuloma absorbed more than 2/3, smooth mucosa, lumen patency; effective: symptoms were significantly relieved, sputum acid-fast bacilli smear improved compared with pre-treatment status (+ + + + reduced by + or above). At the same time, imaging showed absorption of lung lesions < 1/2, absorption of lesions < 2/3 under bronchoscopy, and lumen patency > 1/2. Overall response rate = significantly effective + effective. Ineffective: None of the above criteria were met.

Bacterial negative conversion indicator

Negative conversion indicators after treatment were determined following the 2005 edition of the Guidelines for Clinical Diagnosis and Treatment of Tuberculosis [18]. Sputum smear was examined 3 times a month for acid-fast bacilli, with no acid-fast bacilli observed in sputum smear for 2 consecutive months.

Evaluation of recovery from bronchopathy

The recovery data of bronchial lesions after 6 months of treatment were collected following the relevant criteria [17]: Significantly effective: the absorption of caseous necrosis or granuloma > 2/3, smooth mucosa, lumen patency; effective: absorption of lesions < less than 2/3, lumen patency > 1/2. Overall response rate = significantly effective + effective. Ineffective: None of the above criteria were met.

Criteria for drug withdrawal, observation, and follow-up time

Criteria for discontinuation of anti-TB treatment [18]: Since 96 patients didn't undergo reexaminations via fibro-bronchoscopy after 12 months of treatment, the following criteria for discontinuation were considered as meeting the criteria for "clinically cured". (1) Completing anti-TB treatments for 12 months; (2) Clinical symptoms disappeared; (3) Imaging showed absorption of lung lesions, or residual scars, fibrous cords, or stable calcification; (4) Bronchial stenosis was not aggravated or improved and no atelectasis or lung volume reduction; (5) Negative conversion of sputum. All 96 patients were followed up after discharge until they completed 12 months of treatment.

Statistical analysis

SPSS 26.0 statistical software was used for statistical analysis, the normality test was conducted using the K-S method, with measurement data following normality expressed as mean ± standard deviation (x ± s), and the independent-sample t-test was utilized for group design. Count data were expressed as frequency (n) or rate (%), with the χ^2 test and Fisher's exact test adopted for eligible and ineligible data, respectively. Bilateral $P < 0.05$ was considered statistically significant. Based on the existing sample size and test level, the power of the statistical analysis of this study were calculated by Gpower software to be between 0.76 and 0.82.

Results

General data

The results showed that the study group consisted of 48 patients (M = 21, F = 27), with a mean age of 35.06 ± 10.57 years, while the control group consisted of 48 patients (M = 17, F = 31), with a mean age of 37.85 ± 10.48 years. No significant differences were observed in gender, age, BMI, clinical symptoms, and location of bronchial lesions between the 2 groups ($P > 0.05$), as shown in Table 1.

Comparison of clinical efficacy after 6 months of treatment

The results indicated that after 6-month treatment, the study group included cases of significantly effective ($n = 18$), effective ($n = 22$), and ineffective ($n = 8$), with a response rate of 83.3%, while the control group included cases of markedly effective ($n = 5$), effective ($n = 24$), and ineffective ($n = 19$), with a response rate of 60.4%, with statistically significant differences between the 2 groups ($\chi^2 = 6.235$, $P = 0.013$). See Table 2.

Negative conversion of acid-fast bacilli after 6 months of treatment

The results suggested that after 6 months of treatment, 33 cases in the study group converted negative and 15 cases did not, with a response rate of 68.75%, while 21 cases in the control group converted negative and 27 cases did not, with a response rate of 43.75%, with statistically significant differences in between the 2 groups ($\chi^2 = 6.095$, $P = 0.014$), as shown in Table 3.

Recovery of lesions after 6 months of treatment

The results revealed that after 6-month treatment, the study group included cases of significantly effective ($n = 27$), effective ($n = 14$), and ineffective ($n = 7$), with a response rate of 85.4%, while the control group included cases of significantly effective ($n = 13$), effective ($n = 15$), and ineffective ($n = 20$), with a response rate of 58.3%, and there were significant differences between the 2 groups ($\chi^2 = 8.709$, $P = 0.003$). See Table 4.

Table 1 Comparison of general data

Item	Study Group($n=48$)	Control Group($n=48$)	t/χ^2 value	*P* value
Gender (M/F)	21/27	17/31	0.697	0.404
Age (years)	35.06 ± 10.57	37.85 ± 10.48	-1.299	0.197
BMI (kg/m2)	22.34 ± 2.06	23.03 ± 1.60	-1.832	0.070
Combined with other diseases (*n*)	5	5	0.000	1.000
Clinical symptoms (*n*)				
Cough/expectoration	48	48	-	1.000*
Hemoptysis	12	10	0.236	0.627
Chest tightness/Asthma	11	11	0.000	1.000
Fever	25	18	2.064	0.151
Chest pain	7	6	0.089	0.765
Hoarseness	6	6	0.000	1.000
Site of bronchial lesion (*n*)			-	0.491*
Left main branch	11	6		
Right main branch	12	13		
Left upper	9	7		
Right upper	4	10		
Left Bottom	5	4		
Right lower middle	7	8		
Acid-fast bacilli positive (*n*)	40	42	0.166	0.683
Classification by combined lesions (*n*)			-	1.000*
Inflammatory infiltration	26	26		
Ulcer necrosis	13	12		
Granulation proliferation	6	6		
Cicatricial stenosis	3	4		

Note: *: Using the Fisher's Exact Test

Table 2 Comparison of clinical efficacy after 6 months of treatment

Group	Significantly Effective	Effective	Ineffective	Response Rate(%)
Study($n=48$)	18	22	8	83.3
Control($n=48$)	5	24	19	60.4
χ^2 value			6.235	
P value			0.013	

Table 3 Negative conversion of acid-fast bacilli after 6 months of treatment

Group	Yes	No	Response Rate(%)
Study($n=48$)	33	15	68.75
Contrl($n=48$)	21	27	43.75
χ^2 value		6.095	
P value		0.014	

Table 4 Recovery of lesion after 6 months of treatment

Group	Significantly Effective	Effective	Ineffective	Response Rate(%)
Study($n=48$)	27	14	7	85.4
Control($n=48$)	13	15	20	58.3
χ^2 value		8.709		
P value		0.003		

Recovery of pathological types after 6 months of treatment

The results showed no significant difference in the response rate of inflammatory infiltration (100% VS 100%, $P=1.000$) and granulation proliferation (66.7% VS 0%, $P=0.061$) between the study and control groups after 6 months of treatment. However, the response rate of ulcer necrosis (61.5% VS 16.7%, $P=0.041$) and cicatricial stenosis (100.0% VS 0%, $P=0.029$) in the study group was higher than that in the control group, as shown in Table 5.

Table 5 Recovery of various types of lesions after 6 months of treatment in the 2 groups

Item	Study Group($n=48$)				Control Group($n=48$)				χ^2 value	*P* value
	Significantly Effective	Effective	Ineffective	Response Rate(%)	Significantly Effective	Effective	Ineffective	Response Rate(%)		
Inflammatory infiltration	26	0	0	100.0	13	13	0	100.0	-	1.000*
Ulcer necrosis	1	7	5	61.5	0	2	10	16.7	-	0.041*
Granulation proliferation	0	4	2	66.7	0	0	6	0	-	0.061*
Cicatricial stenosis	0	3	0	100.0	0	0	4	0	-	0.029*

Note: *: Using the Fisher's Exact Test

Table 6 Adverse reactions during treatment

Group	Rash	Stomach discomfort	Abnormal liver function	Incidence(%)
Study ($n=48$)	1	3	5	18.8
Control ($n=48$)	2	3	2	14.6
χ^2 value			0.300	
P value			0.584	

Table 7 Efficacy after 12 months of treatment

Group	Discontinuation	Non-Discontinuation	Response Rate(%)
Study($n=48$)	48	0	100.0
Control($n=48$)	27	21	56.3
χ^2 value		-	
P value		< 0.001*	

Note: *: Using the Fisher's Exact Test

Adverse reactions during treatment

The results indicated rash ($n=1$), stomach discomfort ($n=3$), and abnormal liver function ($n=5$) in the study group, with an incidence of adverse reactions of 18.8%, while the control group included rash ($n=2$), stomach discomfort ($n=3$), and abnormal liver function ($n=2$), with an incidence of adverse reactions of 14.6%, and no significant differences were observed in the incidence of adverse reactions between the 2 groups ($\chi^2=0.300$, $P=0.584$). The relevant adverse reactions in the 2 groups were relieved after symptomatic treatment, as shown in Table 6.

Meanwhile, 9 (18.8%) of the 48 patients who received fibro-bronchoscopic interventional therapy experienced a small amount of local bleeding, and the hemostatic effect was satisfactory after microscopic local injection of epinephrine, without severe bleeding. 4 patients (8.3%) suffered aggravated cough and difficulty in breathing after surgery, which were relieved after symptomatic treatment. Additionally, none reported anesthesia accidents or postoperative infection, and no serious adverse events occurred. In the control group, 48 patients experienced no adverse reactions during both bronchoscopies.

Efficacy after 12 months of treatment

2 of the 48 patients in the study group showed improvement in the degree of stenosis on imaging after 12 months of treatment, with mild airway stenosis remaining without clinical symptoms. Therefore, all patients (100%) met the criteria for treatment discontinuation and were considered clinically cured at the end of the course of treatment. Among the 48 patients in the control group, however, 8 developed significant airway stenosis during treatment and were referred to a higher-level hospital for further treatment. In the meantime, 27 patients (56.3%) met the criteria for discontinuation after 12 months of treatment and were considered clinically cured at the end of the course of treatment, while 13 patients required an extension of treatment to 18 months due to poor recovery of intrapulmonary lesions on imaging. Moreover, the differences between the 2 groups were statistically significant ($P<0.001$), as shown in Table 7.

Discussion

Tracheobronchial tuberculosis (TBTB) is a type of pulmonary tuberculosis that may occur in the mucosa or submucosa of the trachea and bronchi and involve the smooth muscle, cartilage, and adventitia of the trachea. In recent years, the incidence of TBTB has been steadily increasing, and it has been reported that 10-40% of patients with active pulmonary tuberculosis also suffer bronchial tuberculosis, particularly among adolescents and young adults, with a male-to-female ratio of 1:2 to 1:3 [19, 20]. In this study, 96 patients (M = 38, F = 58) were included, with females accounting for 60.4%, and most of the patients were aged 20–30 years, accounting for 30.2%, with young females as the most affected population, consistent with the literature [21, 22]. Young females are

prone to TBTB for numerous reasons, including their socioeconomic status and reluctance to expectorate sputum in public, which is a critical influencing factor [23]. The common sites for bronchial tuberculosis are mainly bronchi, the right middle lobe, the upper lobes of both lungs, and the lingual segment bronchi of the left upper lobe, potentially related to anatomical structures, in which the left main bronchus forms a narrow and slender large angle of about 40–60 degrees with the trachea, making it a more favorable location for the retention of tuberculosis. By contrast, the right main bronchus is characterized by being steep, short, and wide, which facilitates the downward dissemination of tuberculosis [24, 25]. Additionally, the left main bronchus is the most common site for the characteristic manifestations of TBTB, such as cicatricial stenosis, caseous necrosis, and granulation hyperplasia. In this study, the left and right main bronchi were the most affected, consistent with reports from the literature.

Treating TBTB solely with oral anti-TB drugs often exhibits poor efficacy due to a large number of tuberculosis bacteria infiltrating the mucosa and submucosal tissue of the affected areas, leading to substantial pathological changes in the mucosal tissue, such as congestion and edema, often accompanied by nodules, caseous necrosis, and granulomatous necrosis, thus damaging the normal structure of the bronchial wall and leading to the proliferation of fibrous tissue. Moreover, a significant amount of viscous secretions adheres to the surface of the lesions and around them, severely restricting normal blood circulation, which significantly reduces the ability of drugs to penetrate the bronchial-pulmonary barrier, making it difficult to achieve the desired therapeutic effect. This may explain why TBTB is often clinically manifested as an intractable disease that is difficult to cure [26].

Particularly critical in the principles of therapy, early treatment is a crucial guarantee for improving cure rates, reducing drug resistance, and minimizing complications and comorbidities, which is of great significance for improving prognosis [27]. The early pathological changes in TBTB are often reversible, during which the application of fibro-bronchoscopy not only allows for detailed observation of airway lesions but also enables simultaneous treatment. Specifically, this therapy can clear secretions and necrotic substances from the lesion site, improve drainage, and relieve the resulting obstruction, which is beneficial for the repair of affected tissues. In the meantime, systemic chemotherapy combined with local injection via fibro-bronchoscopy can increase the concentration of anti-TB drugs at the lesion site, enhance the bactericidal efficacy, and significantly reduce the toxic side effects of drugs, which allows for better therapeutic effects of anti-TB drugs, promotes the negative conversion of sputum acid-fast bacilli, mitigates complications, preserves lung function, and alleviates patient suffering for patients [28].

In addition to topical administration, fibro-bronchoscopy interventional therapies include treatments such as cryotherapy, laser therapy, microwave therapy, argon knife (argon plasma coagulation), balloon dilation, and stenting. Currently, balloon dilation, argon plasma coagulation, and cryotherapy are the most commonly performed procedures. While cicatricial bronchial stenosis primarily results from fibrosis and hardening of the bronchial walls rather than endobronchial lesions, fibro-bronchoscopic cryotherapy can still provide therapeutic benefits. The freeze-thaw cycle of cryotherapy can induce microvascular damage and controlled necrosis of fibrotic tissue, leading to airway remodeling and partial softening of stenotic areas. Additionally, cryoresection can be performed to remove localized obstructive scar tissue, improving airway patency. Cryotherapy is often used in conjunction with balloon dilation to minimize inflammation and reduce the risk of re-stenosis, making it an effective adjunctive treatment in selected cases of cicatricial stenosis. Reports by CHO et al. [29] indicate a success rate of 73% (82/113) for balloon dilation therapy, while JIN et al. [30] achieved a complete clearance rate of 100% in 41 patients with bronchial stenosis using argon plasma coagulation. Qin Lin et al. [31] have suggested that bronchial cryotherapy combined with balloon dilation is a very safe and effective therapy for airway obstruction due to cicatricial stenosis in bronchial tuberculosis. From the analysis indicators of these studies, the primary goal of using various bronchoscopic techniques to treat TBTB is to remove obstructive lesion tissue from the trachea and bronchi, thereby addressing the issue of tracheobronchial stenosis, while the elimination of pathogens still requires systemic anti-TB chemotherapy (although bronchoscopic topical administration can enhance the effectiveness of chemotherapy to some extent). Moreover, most researchers also proposed that the application of systemic anti-TB therapy combined with topical intratracheal medication and endotracheal interventional therapy exhibits better therapeutic effects, providing a theoretical reference for the implementation of this study [32, 33].

In this study, TBTB patients were given fibro-bronchoscopic cryosurgery combined with topical administration on the basis of conventional anti-TB treatment, and the findings suggested that the clinical efficacy, negative conversion of acid-fast bacilli, and lesion recovery in the study group were superior to those in the control group after 6 months of treatment, indicating that the therapeutic effect of fibro-bronchoscopic cryosurgery combined with topical administration on the basis of conventional anti-TB treatment was superior to conventional therapies, and in the treatment of different lesion types, the study group exhibited better efficacy

in inflammatory infiltration, ulcer necrosis, and cicatricial stenosis than the control group, consistent with relevant studies [30, 32, 33]. However, in the treatment of granulation hyperplasia, no significant differences were observed in the response rate between the study and control groups, which was inconsistent with relevant studies [34], and the statistical results indicated a *P*value very close to 0.05, suggesting that the small sample size may have led to insufficient statistical power. Moreover, after 12 months of treatment, all patients in the study group (100%) reached the criteria for discontinuation and were considered clinically cured at the end of the course of treatment, which was significantly higher than that of the control group (56.2%). Furthermore, the differences between the 2 groups were statistically significant, indicating the great value of fibro-bronchoscopy in the diagnosis and treatment of bronchial tuberculosis [32].

The use of topical treatment via injection of isoniazid, amikacin, levofloxacin, and dexamethasone, as well as aerosol inhalation of isoniazid (0.1 g) and amikacin (0.2 g), is not yet widely adopted in global TB guidelines. However, we believe these approaches offer significant benefits, particularly in targeting localized lesions directly. These methods can potentially enhance therapeutic effects while minimizing systemic side effects. The injection of these antibiotics and corticosteroids into the local lesion site has been explored in preliminary studies for its ability to achieve higher local concentrations of the drugs, which may be beneficial for patients with TBTB. Similarly, aerosolized antibiotics have been considered for their potential to deliver higher doses directly to lung lesions, improving treatment efficacy while minimizing systemic toxicity. Studies have shown that aerosolized antibiotics can enhance therapeutic effects in pulmonary tuberculosis, demonstrating favorable pharmacokinetics and reducing the risk of systemic side effects [35, 36]. While these treatment methods are not yet part of routine clinical practice, they hold promise for improving outcomes, especially in multidrug-resistant or treatment-resistant cases of tuberculosis.

Furthermore, the use of these treatments, along with liver and kidney protection strategies, was approved by the institutional ethics committee to ensure the ethical validity of this treatment protocol, with patient safety and informed consent fully considered. Given the potential hepatotoxic and nephrotoxic effects associated with long-term anti-TB therapy, particularly in patients receiving multidrug-resistant treatments, liver and kidney protection therapies may help minimize organ damage and enhance patient safety. Preliminary studies have suggested that liver protection agents and kidney protection treatments may reduce hepatotoxicity and nephrotoxicity in high-risk populations [37].

However, this study also comes with limitations: (1) The included patients were all enrolled from only one hospital, with regional and population constraints. Meanwhile, there were issues such as a small sample size, a short duration of study, and a limited population, making it necessary to increase the number and range of samples and prolong the duration of study for in-depth observation; (2) Since there were no patients with tracheobronchial wall softening and lymph node fistula who met the exclusion criteria in the time period of interest for this study, further exploration is needed on the therapeutic effects of the study methods on these 2 types of patients. Also, while the combination of bronchoscopic cryotherapy and topical anti-TB management has shown clear clinical benefits in improving AFB conversion rates and lesion recovery, we acknowledge that this novel approach may significantly increase the cost of care. The additional procedures involved, including cryosurgery and topical treatments, require specialized equipment and expertise, leading to higher direct costs. However, we believe that the enhanced treatment outcomes, especially in patients with resistant or difficult-to-treat tuberculosis, may justify the additional investment. Moreover, further research into the long-term economic impact of this approach, including potential reductions in hospital readmissions and prolonged treatment durations, could provide valuable insights into its cost-effectiveness.

Conclusion

In conclusion, the application of fibro-bronchoscopic cryosurgery combined with topical administration on the basis of conventional anti-TB treatments can improve the clinical efficacy of TBTB patients and shorten the duration of treatment without increasing the incidence of adverse treatment reactions. This study provides strong evidence supporting bronchoscopic intervention for TBTB in the treatment phase. However, to confirm the reproducibility and generalizability of these findings, future studies should be conducted in a multicenter setting with multiple bronchoscopists performing the interventions.

Acknowledgements
Not applicable.

Author contributions
Study conception and design: ZYY, LHJ, SJC. Data collection: WKJ, JXG, HGQ. Data analysis and interpretation: PN, QCC, NHY. Drafting of the article: ZYY, SJC, WZX. Critical revision of the article: All authors.

Funding
Wenzhou Science and Technology Bureau Project (2023Y0053).

Data availability
Data is provided within the manuscript.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Wenzhou Central Hospital. We obtained signed informed consent from the participants in this study.

Consent for publication

Not applicable.

Competing interests

All of the authors had no any personal, financial, commercial, or academic conflicts of interest separately.

Received: 28 August 2024 / Accepted: 13 February 2025
Published online: 25 April 2025

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