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RESEARCH ARTICLE

# Bronchoscopic ethanol injection combined with cryotherapy is an effective treatment for benign airway stenosis caused by endotracheal intubation or tracheotomyc

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**Benign tracheal stenosis is a challenge in interventional pulmonary disease. Bronchoscopic ethanol injection (BEI) is always used in airway stenosis caused by malignant tracheal tumours. The efficacy and safety of BEI in benign airway stenosis have not been studied before. To compare safety and efficacy between bronchoscopic cryotherapy and BEI combined with bronchoscopic cryotherapy in the treatment of benign tracheal stenosis. A retrospective study enrolled 61 patients with tracheal stenosis caused by endotracheal intubation and tracheotomy from July 2010 to June 2015. Thirty-three patients who received repeated bronchoscopic cryotherapy alone were included in group A, and 29 patients who underwent repeated cryotherapy combined with BEI were included in group B. The dyspnoea index and tracheal diameter were collected before and after treatment. Efficacy and complications were compared between the two groups. The changes in the tracheal diameter and dyspnoea index before and after treatment were significant in both groups (P<0.05). The long-term cure rate was higher in group B than in group A (100% vs 84.8%). The average duration of dilated airway stability was much shorter in group B than in group A (166±28 days vs 278±32 days, P<0.05). The average number of cryotherapy sessions performed in group B was significantly less than in group A (22.1±4.7 vs 34.9±6.5, P<0.05). Additionally, complications in group A were rare, and the incidence of complications related to BEI was low in group B (mild chest pain, 7.1%; bleeding, 3.6%; and cough, 10.7%). BEI combined with bronchoscopic cryotherapy is an effective minimally invasive choice for relieving airway obstruction symptoms.**

***Keywords:*** Benign tracheal stenosis; Bronchoscopic ethanol injection (BEI); Bronchoscopic cryotherapy

***Abbreviations:*** BEI, Bronchoscopic ethanol injection; TBNA, Transbronchial needle aspiration

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## Introduction

Tracheal stenosis caused by post-intubation care and tracheotomy is common [1]. The treatment of this condition has always been a challenge due to its complex pathophysiology, repeated relapse and various treatment options. Surgical procedures have been the main treatments for benign airway stenosis in the past, but not all patients seem to benefit from surgery [2, 3]. Furthermore, with the rapid development of interventional pulmonology, endoscopic procedures have become a reliable alternative to improve airway patency and avoid resection [4]. Several intervention strategies have been used to relieve the symptoms of obstructed airways [5], such as balloon dilation, stent placement, laser resection,

bronchoscopic ethanol injection (BEI) and bronchoscopic cryotherapy.

Ethanol is a potent sclerosant that can completely destroy epithelial or endothelial cells [6, 7]. Ethanol injection via a bronchoscope has long been used in the treatment of airway stenosis caused by malignant tracheal tumours [8]. Therefore, BEI has the potential to promote granulation tissue and fibrotic tissue necrosis to improve airway stricture. Bronchoscopic cryotherapy, which causes little trauma, is another interventional therapy that can induce necrosis in a selected tissue and destruction of targeted lesions [9] by repeated freeze/thaw cycles. It is one of the techniques available for intracavitary therapy of airway stenosis caused by fibrotic tissue hyperplasia and granulation [10]. Therefore, on the basis of these theories, BEI combined with cryotherapy may have the ability to accelerate the necrosis of fibrotic tissue at a stenotic site to enlarge a narrow lumen.

In this retrospective study, we aimed to review the files of 61 patients with benign tracheal stenosis who underwent cryotherapy combined with BEI or bronchoscopic cryotherapy alone to compare the safety and efficacy of these two procedures.

## Patients and Methods

Sixty-one patients with benign tracheal stenosis were included in this retrospective study. The causes of tracheal stenosis were endotracheal intubation and tracheotomy. All patients underwent bronchoscopy and dimensional reconstruction CT of the neck and chest to identify the location, diameter and length of the stenosis. Patient characteristics are summarized in Table 1. We divided these patients into two groups: the 33 patients who received repeated bronchoscopic cryotherapy alone were placed in group A, and the 29 patients who underwent repeated BEI combined with bronchoscopic cryotherapy were placed in group B. Medical files were reviewed at the Department of Respiratory Medicine, Guizhou Provincial People's Hospital from July 2010 to June 2015. We focused on the immediate effects, durability, complications and long-term cure rate data of the different strategies. This study was approved by the Guizhou Provincial People's Hospital Medical Ethics Committee. All patients signed an informed consent form.

The tracheal diameter and dyspnoea index were collected before and after treatment. The dyspnoea index was scored on the basis of American Thoracic Society dyspnoea rating criteria: level 0: normal; level 1: shortness of breath appears while walking quickly; level 2: shortness of breath appears while walking at an ordinary speed; level 3: stopping normal-speed walking for shortness of breath; and level 4: shortness of breath after mild exercise.

A flexible bronchoscope (Olympus BF-260) was adopted during BEI and cryotherapy. In addition, a transbronchial needle aspiration (TBNA) needle (Olympus) was used for ethanol injection. A Freeze System cryotherapy machine and cryotherapy probe were purchased from ERBE Elektromedizin GmbH (Germany).

All patients inhaled lidocaine before the operation, and then, venous infusion of propofol and remifentanil was performed during the operation. When the bronchoscope was inserted near a stenosis, the TBNA needle was inserted through the working channel of the bronchoscope to pierce the mucosa of the lesion. Then, 0.2 millilitres of ethanol was injected into each lesion site once through the TBNA needle. After all narrowed sites were injected, we removed the TBNA needle and inserted the cryoprobe with its metal probe. Then, the metal probe was touched to the lesion tissue, and repeated freeze/thaw cycles were performed at least 3 times at the lesion site; each freezing step lasted for 1 minute. BEI and cryotherapy were repeated every 4-7 days until the narrow airway was dilated and stabilized. Attention was paid to reducing the chance of haemorrhage during bronchoscopic cryotherapy. To avoid tissue avulsion and bleeding, the probe was not be moved until the tissue had completely melted.

### Statistical Analysis

All analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Measurement data are expressed as the mean ± standard deviation (SD). A paired t test was performed to determine the statistical significance when comparing before and after treatment. For comparisons between the two groups, a two-sample t-test was used. $P < 0.05$ was considered statistically significant.

## Results

When comparing some clinical indicators between the two groups before interventional therapy, there were no obvious differences in the tracheal diameter, dyspnoea index or stenosis lengths (Table 1). The lengths of tracheal stenosis in groups A and B were 1.41±0.22 cm and 1.37±0.14 cm, respectively ($P>0.05$). The tracheal diameters in groups A and B were 5.28±0.28 mm and 5.08±0.24 mm, respectively ($P>0.05$). We compared with dyspnoea index scores between group A and group B, and there was no significant difference (in group A, the average dyspnoea index was 2.50±0.14; in group B, it was 2.52±0.16).

To evaluate the immediate therapeutic effect of bronchoscopic cryotherapy alone and that of BEI combined with cryotherapy, changes in the tracheal diameter and dyspnoea index before and after treatment were compared within each group (Fig. 1). The results showed that diameters of the airways in group A enlarged from 5.28±0.28 mm to 6.73 ± 0.26 mm; the enlargement was much greater in group B, changing from 5.08±0.24 mm to 7.64±0.29 mm. The dyspnoea

**Table 1. Characteristics and clinical indicators.**

| | Group A (n=33) | Group B (n=28) |
|---|---|---|
| Age (Years) | 37.8±6.3 | 35.9±5.5 |
| Male (Female) | 22(11) | 19(9) |
| Endotracheal intubation | 24 | 22 |
| Tracheotomy | 9 | 6 |
| The lengths of the tracheal stenosis (cm) | 1.51±0.22 | 1.37 ±0.14 |
| tracheal diameters | 5.28±0.28cm | 5.08±0.24cm |
| Dyspnea index | 2.50±0.14 | 2.52±0.16 |

The clinical indicators above didn't have statistical difference between the two groups.

**Table 2. The complications and long-term cure rate.**

| Complication | Group A (n=33) | Group B (n=28) |
|---|---|---|
| Incidence | 24.2% | 21.4% |
| Chest pain | 3 | 2 |
| Bleeding | 1 | 1 |
| Cough | 4 | 3 |
| Long-term cure rate | 84.8% | 100% |
| Dumon stent implantation | 3 | 0 |
| surgical resection | 2 | 0 |

The clinical indicators above didn't have statistical difference between the two groups.

index scores changed from 2.50 ±0.14 to 1.25±0.13 in group A and from 2.52 ±0.16 to 1.17±0.14 in group B. All these changes were statistically significant ($P<0.05$).

In addition, the average duration of dilated airway stability and the average number of cryotherapy sessions were analysed and compared between the two groups during the long follow-up period. The results indicated that the average duration of dilated airway stability was much shorter in group B than in group A (166±28 days vs 278±32 days, $P<0.05$) (Fig. 2). A total of 22.1±4.7 cryotherapy sessions were performed in group B, which was significantly less than that in group A (22.1±4.7 vs 34.9±6.5, $P<0.05$) (Fig. 3). Up to two years of follow-up was performed, and the long-term cure rate in group B was 100%. In contrast, the rate was lower in group A (84.8%) because five patients needed other treatments due to aggravated stenosis. Three of these patients received Dumon stent implantation, and two of them underwent surgical resection.

The complications related to cryotherapy in group A included mild chest pain in three patients, cough in four patients and bleeding in one patient (mild chest pain, 9.1%; cough, 12.1%; and bleeding, 3%). In contrast, the complications that appeared in group B were considered to be related to both cryotherapy and BEI and included mild chest pain in two patients, bleeding in one patient and cough in three patients (mild chest pain, 7.1%; bleeding, 3.6%; and cough, 10.7%) (Table 2). In both groups, little bleeding occurred, and it was rapidly stopped by intratracheal instillation of epinephrine. The cough and chest pain were mild and disappeared in seconds after ethanol injection.

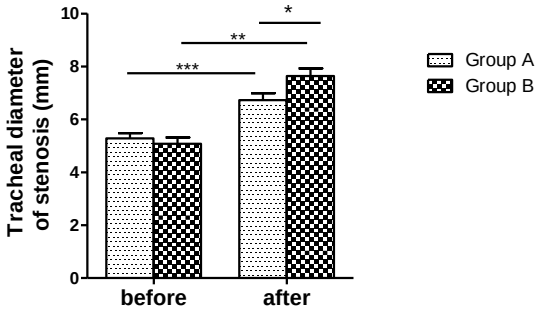


Figure 1**.** Tracheal diameter of stenosis compared in two groups before and after interventional therapy. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$.

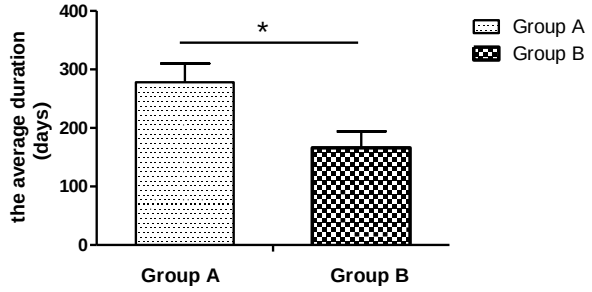


Figure 2**.** Compared the average duration for dilated airways stable between Group A and B. $^{*}P<0.05$.

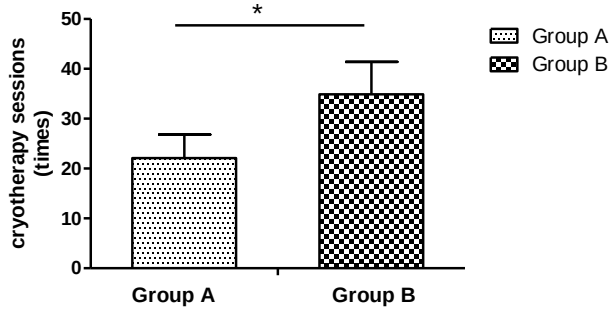


Figure 3**.** Average cryotherapy session performed on each patient were compared in Group A and B. $^{*}P<0.05$.

## Discussion

Tracheal intubation and tracheotomy have important roles in the treatment of critically ill patients. However, benign fibrotic airway stenosis is the most common complication of tracheal intubation and tracheotomy[11]. If the stenosis exceeds a certain critical level, severe dyspnoea, which often requires emergency treatment, may result in respiratory failure and death[12]. Therefore, the treatment of tracheal stenosis is of great significance. A long cycle is unavoidable when using this method to treat benign and malignant airway stenosis; nevertheless, stenosis can easily recur. Given these limitations, exploring alternative methods is necessary. Ethanol is considered an agent for chemical ablation that is widely used in cancers[13]. Injecting ethanol via a bronchoscope has long been reported to be effective in the treatment of airway stenosis caused by malignant tracheal tumours[8]. In this study, we first compared the safety and efficacy of BEI combined with cryotherapy with that of bronchoscopic cryotherapy alone in benign tracheal stenosis due to tracheal intubation and tracheotomy.

In a series of 61 patients, dyspnoea was severe before treatment. By analysing the dyspnoea index, we found that the dyspnoea index decreased after interventional treatment in both groups. Both interventional strategies could eliminate the symptoms of airway obstruction in a short time, suggesting that the immediate effects of BEI combined with cryotherapy and those of bronchoscopic cryotherapy alone were similar. In addition, the incidence of complications in group B (21.1% of patients; included mild chest pain, 7.1%; bleeding, 3.6%; and cough, 10.7%) was not higher than that in group A (23.2% of patients; including mild chest pain, 9.1%; cough, 12.1%; and, bleeding, 3%), showing that BEI combined with cryotherapy did not increase the risk or discomfort of the patients. In other words, this combination was as safe as traditional bronchoscopic cryotherapy alone. Based on these results, we concluded that BEI combined with cryotherapy was safe in the treatment of benign airway stenosis. It is a simple and practical interventional procedure to improve symptoms of a constricted airway.

During the treatment of benign airway stenosis, long-term patency and persistent effects are required, which always affect the choice of interventional procedure. Therefore, in this research, we paid considerable attention to the difference in long-term efficacy between the two interventional treatments. Late outcomes were assessed by patient follow-up visits and follow-up bronchoscopy. The average duration for dilated airway stability, the tracheal diameter and the average number of cryotherapy sessions for each patient were calculated in these two groups. Excitingly, the tracheal diameter in group B was much larger than that in group A after repeated interventional therapy. In addition, restenosis did not recur any more frequently in group B. More importantly, the average duration for dilated airway stability was significantly shorter for patients in group B (166±28 days) than for those in group A (278±32 days, $P<0.05$). Additionally, the patients in group B received an average of 22.1±4.7 cryotherapy sessions until their airway stenosis was stable, whereas patients in group A who underwent bronchoscopic cryotherapy alone needed an average of 34.9±6.5 cryotherapy sessions, which was more sessions. These long-term follow-up results suggested, to a certain extent, that BEI combined with bronchoscopic cryotherapy might be more effective than bronchoscopic cryotherapy alone in patients with benign tracheal stenosis.

In our later analysis, the long-term cure rate was compared between the two groups. The results showed that the long-term cure rate was 100% in group B, which was much higher than the rate in group A (84.8%). After treatment with BEI combined with cryotherapy, restenosis did not occur again in the patients in group B. However, in group A, five patients required other interventional treatment (including Dumon stent implantation (3 patients) and surgical resection (2 patients)) due to airway restenosis. According to this evidence, we reasonably concluded that BEI combined with cryotherapy for benign tracheal stenosis was superior to traditional bronchoscopic cryotherapy alone in regard to therapeutic effects.

## Conclusions

The conclusions of this study are as follows: BEI combined with bronchoscopic cryotherapy is an effective minimally invasive choice for relieving airway obstruction symptoms. In some cases, this combination is superior to bronchoscopic cryotherapy alone in the treatment of benign airway stenosis caused by tracheal intubation and tracheotomy. BEI combined with bronchoscopic cryotherapy is safe and effective, and it is worthy of clinical application.

## Ethics Approval

Ethical approval was granted from the ethics committee of Guizhou Provincial People's Hospital.

## Patient Consent for Publication

A written informed consent was obtained from the patient for publication of the information about them that appears within this case report.

## Conflicting Interests

The authors declare that they have no conflict of interests.

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