Nonstent Combination Interventional Therapy for Treatment of Benign Cicatricial Airway Stenosis

Xiao-Jian Qiu, Jie Zhang, Ting Wang, Ying-Hua Pei, Min Xu

Department of Pulmonary Medicine, Beijing Tian Tan Hospital, Capital Medical University, Beijing 100050, China

Abstract

Background: Benign cicatricial airway stenosis (BCAS) is a life-threatening disease. While there are numerous therapies, all have their defects, and stenosis can easily become recurrent. This study aimed to investigate the efficacy and complications of nonstent combination interventional therapy (NSCIT) when used for the treatment of BCAS of different causes and types.

Methods: This study enrolled a cohort of patients with BCAS resulting from tuberculosis, intubation, tracheotomy, and other origins. The patients were assigned to three groups determined by their type of stenosis: Web-like stenosis, granulation stenosis, and complex stenosis, and all patients received NSCIT. The efficacy and complications of treatment in each group of patients were observed. The Chi-square test, one-factor analysis of variance (ANOVA), and the paired *t*-test were used to analyze different parameters.

Results: The 10 patients with web-like stenosis and six patients with granulation stenosis exhibited durable remission rates of 100%. Among 41 patients with complex stenosis, 36 cases (88%) experienced remission and 29 cases (71%) experienced durable remission. When five patients with airway collapse were eliminated from the analysis, the overall remission rate was 97%. The average treatment durations for patients with web-like stenosis, granulation stenosis, and complex stenosis were 101, 21, and 110 days, respectively, and the average number of treatments was five, two, and five, respectively.

Conclusions: NSCIT demonstrated good therapeutic efficacy and was associated with few complications. However, this approach was ineffective for treating patients with airway collapse or malacia.

Key words: Benign Airway Stenosis; Bronchoscopy; Complications; Efficacy; Interventional Therapy

Introduction

Benign cicatricial airway stenosis (BCAS) is a life-threatening disease which can result from tracheal intubation, tracheotomy, tracheobronchial tuberculosis, tracheobronchial anastomosis, chest trauma, stent implantation or inhalation injury. The most common causes are tracheal intubation and tracheotomy, as BCAS occurs following 19% and 65% of these procedures, respectively.[1,2] Unlike the United States and Europe, the main cause of benign airway stenosis (BAS) in China is tuberculosis, which accounts for 64.25% of BAS cases, followed by tracheal intubation and tracheotomy (15.03% of BAS cases).[3] While surgical reconstruction is the gold standard treatment for symptomatic BAS, the condition can be deemed inoperable due to the presence of long strictures, inflammation, or when BAS occurs after lung transplantation or in patients with poor respiratory or cardiovascular status.[4] BCAS can be divided into three types.[5] Web-like stenosis refers to an abrupt transition of an annular lesion which occurs as a result of simple cicatricial hyperplasia. Granulation stenosis refers to a luminal stenosis caused by intraluminal hyperplasia of granulation tissue. Complex stenosis refers to any type of stenosis except for the above-mentioned two types, and generally occurs concurrent with cicatrix and granulation tissue hyperplasia, and sometimes concurrent with airway malacia or collapse. Complex stenosis cannot be effectively resolved by using a high frequency electric knife or balloon dilatation, and eventually progresses to refractory airway stenosis, which is often treated by silicone stent implantation.[6,7] However, stent implantation can result in complications such as stent migration, hyperplasia of granulation tissue, formation of ulcerative tissue around the stent, and ischesis in the stent,[4] which can sometimes require emergency interventional bronchoscopic therapy. Repeated recurrence of refractory airway stenosis after treatment is the major cause of failed treatment, and occurs in 40–70% of cases.[8] We found that treatment itself could cause airway injuries, and especially during heat coagulation (including electric coagulation, argon plasma coagulation, and laser) and stent implantation.[9] In recent

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.162496

Address for correspondence: Dr. Jie Zhang, Department of Pulmonary Medicine, Beijing Tian Tan Hospital, Capital Medical University, Beijing 100050, China
E-Mail: zhangjie6218@163.com

years, the above-mentioned approaches have been avoided and replaced by nonstent combination interventional therapy (NSCIT), in which mechanical balloon expansion and cryotherapy are combined, and produce only minor damage to the airway. When necessary, an electric needle knife with a tiny cross-section of electric coagulation is used to remove the scar,[10] and in some patients with repeated cicatricial hyperplasia, mitomycin or paclitaxel is used to inhibit formation and recurrence of cicatrix.[8,11-15] This study was conducted to examine the therapeutic efficacy of NSCIT.

Methods

Patients

A cohort of patients with BCAS who were treated in the Department of Respiratory Diseases, Beijing Tiantan Hospital, Capital Medical University between January 2009 and April 2013 were enrolled in this study. All patients provided a signed informed consent giving permission for their participation in this study and use of their medical data. The protocol for this study was approved by the Institutional Ethics Committee of Beijing Tian Tan Hospital, Capital Medical University. The patients included in the study satisfied the following two criteria for eligibility: (1) Aged 18–70 years and diagnosed as BCAS; (2) no severe heart or lung dysfunctions. The study exclusion criteria were as follows: (1) The presence of a benign tumor; (2) noncicatricial hyperplasia, such as relapsing polychondritis or amyloidosis; (3) patients with severe airway stenosis or an occlusion unsuitable for interventional therapy. A total of 64 patients with BCAS resulting from tuberculosis, tracheal intubation/tracheotomy, and other origins (trauma, end-to-end anastomosis, and stent removal, etc.) were enrolled in the study. There were two patients with airway stenosis after removal of a metal stent. The first patient received a stent for tracheotomy, and the other for tuberculosis. One to four therapies, which were selected based on the type of lesion, were used in combination as NSCIT. A total of seven patients withdrew from the study (three patients were lost to follow-up after one session of treatment; three patients died of accidents due to delayed visits, and one patient refused to continue with treatment); therefore, the results from 57 patients were analyzed [Table 1]. Three patients died from accidents resulting from poor compliance due to their economic and living situations (e.g., living a long distance from a hospital or experiencing transportation problems, etc.) as well as giving inadequate attention to their medical condition. These patients did not comply with their follow-up schedule and died of acute asphyxia. However, their deaths were not attributable to poor treatment efficacy. Instead, their first treatment produced good results, but the airway stenosis became recurrent, and they died after not seeking a second treatment in a timely manner. As seen in Table 1, there were no statistically significant differences in age, gender, affected site or etiological factors among patients with different types of BCAS.

Table 1: General characteristics of the enrolled patients with benign cicatricial airway stenosis

Characteristics	Web-like stenosis	Granulation stenosis	Complex stenosis	*P*
Age (years, mean ± SD)	34.7 ± 12.0	39.0 ± 22.2	37.5 ± 16.1	0.848
Gender, *n* (%)				0.151
Male	7 (70)	4 (67)	16 (39)	
Female	3 (30)	2 (33)	25 (61)	
Sites, *n* (%)				0.378
Trachea	7 (70)	5 (83)	18 (44)	
Left principal bronchus	2 (20)	1 (17)	17 (42)	
Right principal bronchus	0	0	4 (10)	
Bronchus intermedius	1 (10)	0	2 (5)	
Etiological factors, *n* (%)				0.167
Posttuberculosis	3 (30)	0	21 (51)	
Posttracheal intubation and posttracheotomy	5 (50)	4 (67)	13 (32)	
Other origins	2 (20)	2 (33)	7 (17)	
Total, *n* (%)	10 (100)	6 (100)	41 (100)	

SD: Standard deviation.

Procedures

Anesthesia selection was based on the patient's age and severity of the disease. Local anesthesia + sedation and analgesia consisted of 2% lidocaine + midazolam and fentanyl. General anesthesia was administered by an anesthesiologist using a regimen of propofol, midazolam, remifentanil, and muscle relaxants in an operating room.

Sources of materials used in interventional procedures:

- Devices: (1) Balloon dilator: Boston Scientific Company, Boston, MA, USA; (2) Needle knife: MTW Company, Germany; (3) High frequency electronic equipment: ERBE Company Tübingen, Germany; (4) Cryotherapy equipment: ERBE Company, Germany; (5) Local instillation catheter: Self-made, 125-cm length and 2-mm diameter.
- Drugs: (1) Mitomycin (10 mg/bottle, Zhejiang Hisun Pharmaceutical Co., Ltd., China); 0.4 mg/ml × 1 ml/cm; (2) Paclitaxel (30 mg/bottle, Beijing Union Pharmaceutical Factory, China), 0.8 mg/ml × 1 ml/cm.

Therapeutic regimens:

- Regimen 1: A balloon dilator was initially used to expand the stenosis. If the scar was too tough to expand, a high frequency electric needle knife was used to cut the scar open and apply cryotherapy to the basilar portion of the scar. For granulation tissue, a high frequency electric needle knife was used to remove the lesion and then apply cryotherapy to its basilar portion.
  If the scar was too tough to expand, a needle knife was used to make a radial incision into the scar tissue, while avoiding its membranous parts. Sites for cryotherapy were determined by the location of residual scar and granulation tissue. Treatment was given at sites located 5 mm apart, and each site received three cycles of a one-minute freeze-thaw regimen.

- Regimen 2: In cases of repeatedly recurring stenosis (stenosis which reoccurs after three previous treatment sessions), topical mitomycin or paclitaxel was administered using a self-made local instillation catheter,[13] after each session of interventional therapy [Figure 1a].

Response assessment

While there is currently no consensus regarding the criteria that should be used for assessing a patient's response to treatment of BAS,[16,17] we used the following criteria based on their practicality for use in evaluating clinical effects: (1) Durable remission: Duration of airway patency was >6 months, without the need for further treatment; (2) Remission: Duration of airway patency was 3–6 months, and may have required additional therapy; (3) No remission: Duration of airway patency was <3 months, and required additional treatment; (4) Failure: Unable to maintain airway patency, concurrent with airway malacia or collapse.

Complications and their severity

In this study, only complications directly related to the therapy and medications used to treat airway stenosis were included statistical analyses. The effects of topical drug administration on white blood cells (WBCs), as well as liver and kidney function were also monitored.

Statistical analysis

All statistical analyses were performed using SPSS for Windows, Version 16.0. SPSS Inc., Chicago, IL, USA. Results of analyses of normally distributed data are presented as the mean ± standard deviation (SD), while results of numerical data analyses are presented as frequency. The Chi-square test was used to analyze the following parameters: The etiological factors for different types of BAS; the efficacy of different types of interventional therapy; the efficacy of interventional therapy in treating airway stenosis of different origins; the relationship between the type of drug used and efficacy. One-factor analysis of variance (ANOVA) was used to analyze the duration and number of treatments required for airway stenosis of different types and origins. The paired *t*-test was used to analyze WBC levels, as well as liver and renal functions before and after treatment; $P < 0.05$ were considered statistically significant.

Results

Therapeutic effects of interventional bronchoscopic therapy for different types and origins of BCAS

The therapeutic effects of interventional bronchoscopic treatment on different types of BCAS are summarized in Table 2. Among 10 patients with web-like stenosis and six patients with granulation stenosis, all 16 patients (100%) experienced a durable remission. Among 41 patients with complex stenosis, 29 (71%) experienced durable remission, and 36 (88%) experienced a remission. However, none of the five patients with airway malacia in that group experienced a durable remission. Among 24 patients with airway stenosis after tuberculosis, 16 (67%) experienced durable remission, and 22 (92%) experienced remission. A durable remission rate of 76% (16/21) and remission rate of 100% (21/21) were achieved after eliminating three patients with airway malacia. Among 22 patients with airway stenosis after intubation and tracheotomy, 18 (82%) experienced durable remission, and 19 (86%) experienced remission. However, after eliminating two patients with airway malacia, the durable remission rate

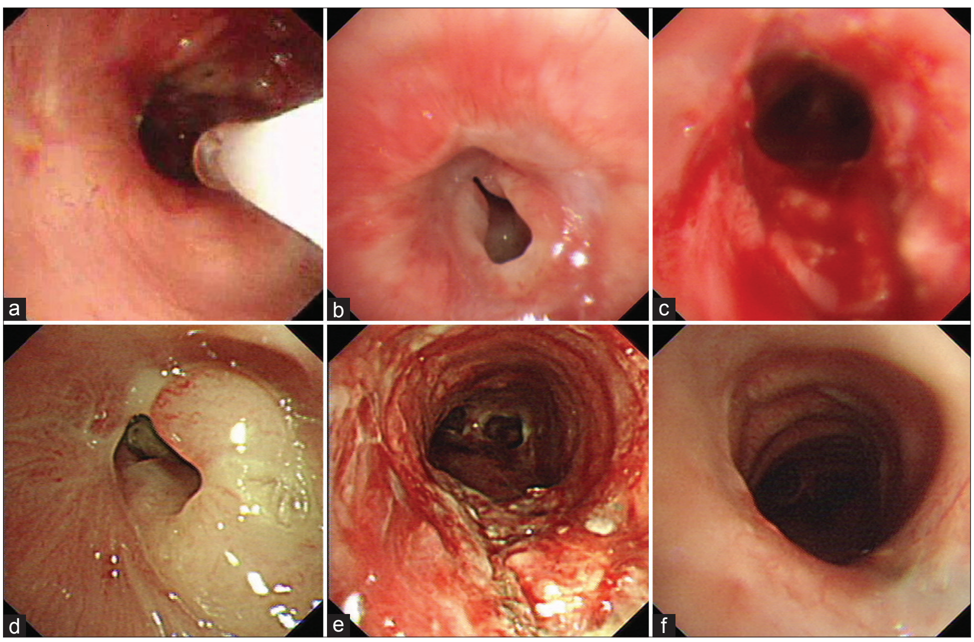

Figure 1: Local catheter instillation (a); prior to the first treatment session (July 13, 2010) (b); after the first treatment session (July 13, 2010) (c); prior to the third treatment session (September 1, 2010) (d); after the third treatment session (September 1, 2010) (e); after 1 year (November 15, 2011) (f).

of 90% (18/20) and the remission rate of 95% (19/20). All 11 patients (100%) with airway stenosis of other origins experienced a durable remission.

Seven patients with complex stenosis satisfied the criteria for remission, and these included six patients who did not complete the 6 months of observation period. The remaining patient was a 54-year-old female with airway stenosis after tuberculosis. In that patient, the duration of airway patency was >3 months, even though the lesion measured 2.2 cm in length. However, her airway stenosis repeatedly re-occurred, and she failed to meet the criteria for a durable remission. Bronchoscopy showed partial airway malacia, and surgery or stent therapy was recommended.

Two patients with complex stenosis showed no remission. In the first case, a 40-year-old female experienced airway stenosis after tracheal intubation and presented with a lesion measuring 2 cm in length. She was placed on a once-every-2-week NSCIT regimen, but failed to maintain airway patency. Surgery was recommended after taking into account evidence of airway malacia shown by bronchoscopy. In the second case, a 31-year-old male patient developed airway stenosis after tracheotomy, and presented with a lesion measuring 2 cm in length. He was placed on a once-every-2-week NSCIT regimen for 2 months, but failed to show satisfactory results. Topical paclitaxel was administered and the treatment interval was extended to 1.5 months; however, airway stenosis still recurred on a frequent basis, and surgery was recommended.

Three patients diagnosed as complex stenosis failed treatment with NSCIT. The first patient was a 53-year-old male who experienced airway stenosis after tracheal intubation, and developed a lesion measuring 3 cm in length. The second patient was a 16-year-old female who experienced tracheal stenosis after tuberculosis and had a lesion 3 cm in length. The third patient was a 54-year-old female who developed left principle bronchial stenosis after tuberculosis. Because all three of these patients failed to maintain airway patency after balloon dilatation, and bronchoscopy showed evidence of airway malacia, they were judged to have failed treatment. Statistical analyses stratified by two layers of remission and no remission showed no significant differences in the therapeutic effects of NSCIT when used to treat BCAS of different origins [Table 2].

Effects of topical drugs used for treating patients with BCAS

Among the seven patients who received treatment with mitomycin, all seven experienced a durable remission. Among 31 patients treated with paclitaxel, 26 experienced a durable remission, one experienced a remission, two experienced no remission, and two other patients failed treatment. Statistical analyses stratified by two layers of remission and no remission showed no significant differences regarding the therapeutic effects of different drugs used to treat patients with BCAS.

Duration and number of treatments required for durable remission of BCAS of different types and origins.

There were no statistically significant differences in the duration or number of treatments required to achieve a durable remission of BCAS of different types and origins [Table 3].

For patients with web-like stenosis, the average duration of treatment was 101 days, and the average number of

Table 3: Duration and number of treatments required to achieve a durable remission of BAS of different types and origins

Items	Duration of treatment (days)	*P*	Number of treatments	*P*
Types		0.131		0.051
Web-like stenosis	101 ± 84		4.6 ± 3.3	
Granulation stenosis	21 ± 21		1.8 ± 0.4	
Complex stenosis	110 ± 107		5.5 ± 3.5	
Origins		0.628		0.871
Posttuberculosis	106 ± 118		4.7 ± 2.0	
Posttracheal intubation and posttracheotomy	79 ± 92		4.6 ± 4.2	
Other origins	110 ± 78		5.3 ± 3.7	

BAS: Benign airway stenosis.

Table 2: Therapeutic effects of interventional bronchoscopic therapy for different types and origins of BCAS

Items	Durable remission (*n*)	Remission (*n*)	No remission (*n*)	Failure (*n*)	Total (*n*)	Cure rate (%)	Remission rate (%)	*P*
Type								0.343
Web-like stenosis	10	0	0	0	10	100	100	
Granulation stenosis	6	0	0	0	6	100	100	
Complex stenosis								
No airway malacia	29	6	1	0	36	81	97	
Airway malacia	0	1	1	3	5	0	20	
Origin								0.424
Posttuberculosis (airway malacia)	16	6 (1)	0	2 (2)	24	67	92	
Posttracheal intubation and posttracheotomy (airway malacia)	18	1	2 (1)	1 (1)	22	82	86	
Other origins	11	0	0	0	11	100	100	

BCAS: Benign cicatricial airway stenosis.

treatments was five. For granulation stenosis, the average duration of treatment was 21 days and the average number of treatments was approximately two. For complex stenosis, the average duration of treatment was 110 days and the average number of treatments was approximately five.

The longest period of interventional therapy required to achieve a durable remission of complex stenosis without topical drug administration was 123 days, and occurred in a 48-year-old female who developed airway stenosis after end-to-end anastomosis of the trachea. She experienced a durable remission after receiving two sessions of high frequency electric knife therapy, three sessions of balloon dilation, and four sessions of cryotherapy. The first session of therapy was performed on July 13, 2010, and consisted of needle electric knife + balloon dilatation + cryotherapy [Figure 1b and c]. One month later, a radiological examination showed evidence of a web-like neoplasm, and the 2nd session of treatment (August 10, 2010) was performed using forceps + cryotherapy. Twenty days later, recurrence was again observed, and a third session of treatment was performed (September 1, 2010) using needle electric knife + balloon dilatation + cryotherapy [Figure 1d and e]. However, 2.5 months later, another recurrence was observed, and a fourth session of treatment was performed (November 16, 2010) using balloon dilatation + cryotherapy. After the fourth treatment session, regular monitoring showed the patient to have a stable scar that did not require further treatment, and her condition was considered to be a durable remission. The patient returned for a follow-up visit 1-year later, at which time the airway had maintained its patency (November 15, 2011) [Figure 1f].

Among complex airway stenosis patients who satisfied the criteria for durable remission with local drug administration, a 26-year-old woman received the longest duration of treatment. The woman developed left principal bronchial stenosis after tuberculosis, and received 413 days of treatment before being cured. Her treatments included 8 sessions of balloon dilation, 8 sessions of cryotherapy, and 6 sessions of local drug administration.

Complications

All patients in our study experienced some type of complication. For example, small amounts of necrotic tissue remained on the wound surface, regardless of drug administration. However, no patient experienced an acute airway obstruction requiring emergency surgery, and no airway bronchomalacia or perforation related to the interventional therapy was observed after the treatments were completed. In addition, WBC counts and levels of alanine transaminase, aspartate transaminase, and creatinine before and after local drug administration were compared, and showed no statistically significant differences [Table 4].

Table 4: WBCs, ALT, AST, and creatinine in patients with local drug administration before and after treatment

Items	Before treatment	After treatment	*P*
WBC (10^9/L)	5.87 ± 1.60	6.19 ± 1.75	0.440
ALT (U/L)	12.26 ± 6.35	12.44 ± 5.26	0.909
AST (U/L)	15.12 ± 3.51	14.18 ± 4.57	0.455
Creatinine (μmol/L)	53.72 ± 13.08	53.59 ± 11.55	0.943

WBCs: White blood cells; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

Discussion

Benign cicatricial airway stenosis is mainly treated by surgery and interventional therapy, and surgical reconstruction remains the gold standard for treatment of BAS associated with intubation.[18] Based on clinical observations, the remission rate of BCAS has been reported to be 91.9%, the failure rate 5.3%, the mortality rate 2.6%, and the complication rate 39%.[19] The presence of a lesion measuring ≥50% the length of the trachea is an absolute contraindication for surgery. Other contraindications include subglottic stenosis, inflammation, nerve injury, and cardiovascular failure.[20] In those cases, interventional therapy is the proper treatment, and usually involves stent implantation. Success rates of 26.6–27.2% and a mean treatment time of 259 ± 173 days have been reported for patients treated with a silicone stent.[6,21] However, several problems can be encountered when using silicone stents.[21-24] Stent migration, granulation tissue hyperplasia, and mucus retention resulting in airway obstruction occur in 9.5–17.5%, 6–28.21%, and 3.6–6.3% of stented patients, respectively. In addition, the thick wall and relatively small inner diameter of the silicone stent contradicts its use for treating irregular airway stenosis.[4] Patients also need to be repeatedly hospitalized to adjust the stent, with high rates of complications.

In addition to stent implantation, laser therapy, electrocautery, APC, and balloon dilatation have also previously been used to treat airway stenosis. Although these approaches may cure some cases of BAS, the recurrence rate is extremely high, and patients are subsequently forced to undergo stent implantation. However, as mentioned earlier, the success rate of stent implantation is not high,[6] and identifying the proper treatment for BAS has remained a difficult problem. Both clinical and animal studies have reported that use of electric coagulation enlarged the airway injury, extended the lesion, and induced additional restenosis, all of which can lead to airway malacia and eventual treatment failure.[9,10] Therefore, we noticed that stenosis recurrence was also related to the presence of a tracheal injury resulting from the intervention itself. Thermal coagulation therapies can severely injure the airway mucosa and cartilage, leading to airway restenosis, and treatment failure. However, we found that mechanical expansion and cryotherapy caused little damage to airway mucosa and spared the airway cartilage. The recurrence rate of airway stenosis is low.[10,11] A group of patients with BCAS and receiving electric coagulation therapy showed a remission rate of only 8.33%.[10] Since 2008, we have mainly used the above-mentioned therapeutic regimens, and as a result, the airway stenosis recurrence rate has decreased and the remission rate has been 82.34%.[10] In some patients with repeated tracheal scar tissue hyperplasia, the inner diameter of the airway cannot be maintained by repeated interventional therapy. Because the therapeutic effect of airway stents is limited, the use of medications should be considered to inhibit airway scar tissue hyperplasia in such patients.

Scar hyperplasia is a common problem encountered in many areas of medicine, and the local application of drugs represents an important method of controlling such hyperplasia. Drugs used for inhibiting airway scar hyperplasia include mitomycin, paclitaxel, immunosuppressants, and antibiotics;[25] however, topical application of mitomycin for airway cicatricial stenosis has received the greatest attention.[26-30] Paclitaxel has been used to prevent restenosis associated with coronary stenting. A paclitaxel coated coronary stent can provide localized release of paclitaxel within the coronary artery vessel wall, thereby inhibiting hyperplasia of vascular intima scar tissue.[31] In addition, some scholars speculate that paclitaxel-eluting stents can be implanted in the airway to inhibit proliferation of granulation tissue. In 2006, Choong *et al*. showed that a paclitaxel-eluting stent significantly inhibited the growth of granulation tissue, and thereby extended airway bypass stent patency time.[15] Wang *et al*. and Chen *et al*. showed that paclitaxel had an inhibitory effect on human embryonic lung fibroblast cells, and thus provided a theoretical basis for application of paclitaxel.[32,33] In addition, an animal study conducted by Wang *et al*.[14] also confirmed the efficacy of paclitaxel for inhibiting the growth of scar tissue.

In our study, some patients with repeatedly recurring airway stenosis after balloon dilatation and cryotherapy received topical treatment with mitomycin or paclitaxel in the tracheal stenosis area to inhibit hyperplasia of scar and granulation tissue. In addition, we showed a remission rate of 87.8% and durable remission rate of 70.7% among patients with complex airway stenosis. Furthermore, after eliminating airway malacia patients, the remission rate increased to 97.22% (35/36). When taking into account that six patients in remission had maintained their airway patency for >3 months, and were most likely to achieve durable remission, the durable remission rate for nonmalacia complex airway stenosis was ~97%, and the durable remission rates for web-like stenosis and granulation stenosis reached 100%. These results are better than those obtained when implanting a Dumon stent, and were achieved without obvious complications.[6,21]

We also observed that after eliminating airway malacia patients, the remission rate for airway stenosis after tuberculosis was 100% (21/21), and the durable remission rate was 76.2% (16/21). The remission rate for airway stenosis occurring after intubation and tracheotomy was 95% (19/20), and the durable remission rate was 90% (18/20). The durable remission rate for airway stenosis of other origins was 100% (11/11). No statistically significant differences were found among these different durable remission rates, suggesting that NSCIT can obtain satisfactory results in treating various types of airway stenosis, despite their different causes. We found that mitomycin and paclitaxel had equivalent efficacies for inhibiting scar tissue hyperplasia. However, most patients who received paclitaxel were treated during a later phase of this study, and in the early phase, only a few patients were treated with mitomycin. Therefore, a further investigation is required to explore whether these two drugs may have different effects.

We found that the method employed for topical administration of drugs was related to their therapeutic effects. While various methods of local administration exist (inhalation, local cotton swabbing, local mucosal injection, etc.), the ideal method would permit accurate positioning, and be able to ensure that the proper dose of drug is administered to the mucosa of the airway stenosis segment. When using an inhalation method, it is very difficult to determine the actual dose and concentration of the drug received by the target tissue. Patients need to inhale a high dose of drug to achieve the ideal local concentration, which can result in systemic side effects. Likewise, it is difficult to calculate the amount of drug delivered to a tissue when using a cotton swab, because a large amount of drug can be absorbed by the swab material.[34] While local mucosal injection can deliver an accurate quantity of the drug, scar tissue has a high density, making the drug delivery procedure very difficult to perform.[35] Therefore, we utilized a self-made catheter to enable the localized administration of drugs.[13] An ordinary lavage catheter tip is obstructed and has a tiny opening in its side which allows only one drop of liquid to exit, ensuring good absorption by the airway mucosa. It can also prevent liquid from flowing into the normal airway, thus, making it possible to achieve precise dosing of the airway mucosa. Based on the literature and our research results,[11,12,32,33] the local concentrations of mitomycin and paclitaxel administered to the treated mucosal tissue were 0.4 mg/ml and 0.8 mg/ml, respectively. The total dose was calculated using the stenosis length, and an assumed absorption of 1 ml/cm.

Our study shows that when using balloon dilatation to treat airway stenosis, it may be necessary to utilize an electric needle knife to cut the scar or remove granulation tissue, and use cryotherapy to manage any residual scar and granulation tissue after expansion, and thereby assist in preventing recurrence of airway stenosis. This treatment regimen can produce a durable remission in most patients, and especially in those with web-like stenosis and granulation stenosis. In some patients with repeated recurrence of airway stenosis, as well as in most cases of complex stenosis, local application of mitomycin or paclitaxel inhibits proliferation of scar tissue, reduces the stenosis recurrence rate, and eventually allows the patient to achieve a durable remission. None of the patients who received NSCIT in our study underwent stent implantation, and most experienced a durable remission. From the study, we can see that NSCIT demonstrated good therapeutic effects and was associated with few complications.

It should be noted that some patients with repeatedly recurring airway stenosis may require additional cycles of NSCIT and prolonged durations of treatment, and thus the financial costs associated with NSCIT can be high. However, as shown in this study, such patients can achieve a durable remission with fewer complications. Additional studies with larger numbers of patients are required to further confirm the efficacy and safety of NSCIT. Finally, NSCIT was found to be ineffective in patients with airway collapse or malacia, where surgery or airway stent implantation is still recommended.

Our study showed that all patients with BCAS without accompanying airway collapse or malacia are suitable for NSCIT. Furthermore, NSCIT demonstrated good therapeutic efficacy and was associated with few complications. However, this approach is ineffective when treating patients with airway collapse or malacia, and either surgery or airway stent implantation is still recommended in such cases.

Acknowledgments

We thank Juan Wang, Yu-Ling Wang, and Chen-Yang Zhang for their assistance in conducting experiments and collecting data.

References

1. Lorenz RR. Adult laryngotracheal stenosis: Etiology and surgical management. Curr Opin Otolaryngol Head Neck Surg 2003;11:467-72.
2. Stauffer JL, Olson DE, Petty TL. Complications and consequences of endotracheal intubation and tracheotomy. A prospective study of 150 critically ill adult patients. Am J Med 1981;70:65-76.
3. Li YQ, Li Q, Bai C, Huang Y, Zhao LJ, Yao XP, *et al.* Causes of benign central airway stenoses and the efficacy of interventional treatments through flexible bronchoscopy (in Chinese). Chin J Tuberc Respir Dis 2008;31:364-8.
4. Tsakiridis K, Darwiche K, Visouli AN, Zarogoulidis P, Machairiotis N, Christofis C, *et al.* Management of complex benign post-tracheostomy tracheal stenosis with bronchoscopic insertion of silicon tracheal stents, in patients with failed or contraindicated surgical reconstruction of trachea. J Thorac Dis 2012;4 Suppl 1:32-40.
5. Freitag L, Ernst A, Unger M, Kovitz K, Marquette CH. A proposed classification system of central airway stenosis. Eur Respir J 2007;30:7-12.
6. Terra RM, Bibas BJ, Minamoto H, Waisberg DR, Tamagno MF, Tedde ML, *et al.* Decannulation in tracheal stenosis deemed inoperable is possible after long-term airway stenting. Ann Thorac Surg 2013;95:440-4.
7. Agarwal R, Khan A, Aggarwal AN, Singh N, Bhagat H, Kumar B, *et al.* Initial experience of endobronchial silicon stents from a tertiary care centre in North India. Indian J Chest Dis Allied Sci 2011;53:93-8.
8. Smith ME, Elstad M. Mitomycin C and the endoscopic treatment of laryngotracheal stenosis: Are two applications better than one? Laryngoscope 2009;119:272-83.
9. Zhang J, Wang T, Wang J, Pei YH, Xu M, Wang YL, *et al.* Effect of three interventional bronchoscopic methods on tracheal stenosis and the formation of granulation tissues in dogs. Chin Med J 2010;123:621-7.
10. Zhang J, Wang J, Wang T, Xu M, Dang BW, Pei YH, *et al.* A pilot study on interventional bronchoscopy in the management of airway stenosis with benign hyperplasia (in Chinese). Chin J Tuberc Respir Dis 2011;34:334-8.
11. Ubell ML, Ettema SL, Toohill RJ, Simpson CB, Merati AL. Mitomycin-c application in airway stenosis surgery: Analysis of safety and costs. Otolaryngol Head Neck Surg 2006;134:403-6.
12. Chen N, Zhang J, Xu M, Wang YL, Pei YH. Inhibitory effect of mitomycin C on proliferation of primary cultured fibroblasts from human airway granulation tissues. Respiration 2013;85:500-4.
13. Cui J, Zhang J, Wang J, Xu M, Pei YH, Wang T, *et al.* Effect of topical application with mitomycin C in the management of benign cicatricial airway stenosis (in Chinese). Chin J Tuberc Respir Dis 2012;35:901-6.
14. Wang LH, Zhang J, Chen N, Zhang YY, Xu M, Yue YM. The pilot study of the effect of paclitaxel by local application on scar formation after airway injury in rabbits (in Chinese). Chin J Tuberc Respir Dis 2013;36:202-6.
15. Choong CK, Phan L, Massetti P, Haddad FJ, Martinez C, Roschak E, *et al.* Prolongation of patency of airway bypass stents with use of drug-eluting stents. J Thorac Cardiovasc Surg 2006;131:60-4.
16. Iwamoto Y, Miyazawa T, Kurimoto N, Miyazu Y, Ishida A, Matsuo K, *et al.* Interventional bronchoscopy in the management of airway stenosis due to tracheobronchial tuberculosis. Chest 2004;126:1344-52.
17. Shitrit D, Valdsislav P, Grubstein A, Bendayan D, Cohen M, Kramer MR. Accuracy of virtual bronchoscopy for grading tracheobronchial stenosis: Correlation with pulmonary function test and fiberoptic bronchoscopy. Chest 2005;128:3545-50.
18. Marel M, Pekarek Z, Spasova I, Pafko P, Schutzner J, Betka J, *et al.* Management of benign stenoses of the large airways in the university hospital in Prague, Czech Republic, in 1998-2003. Respiration 2005;72:622-8.
19. Donahue DM, Grillo HC, Wain JC, Wright CD, Mathisen DJ. Reoperative tracheal resection and reconstruction for unsuccessful repair of postintubation stenosis. J Thorac Cardiovasc Surg 1997;114:934-8.
20. Puma F, Ragusa M, Avenia N, Urbani M, Droghetti A, Daddi N, *et al.* The role of silicone stents in the treatment of cicatricial tracheal stenoses. J Thorac Cardiovasc Surg 2000;120:1064-9.
21. Martinez-Ballarin JI, Diaz-Jimenez JP, Castro MJ, Moya JA. Silicone stents in the management of benign tracheobronchial stenoses. Tolerance and early results in 63 patients. Chest 1996;109:626-9.
22. Hu HC, Liu YH, Wu YC, Hsieh MJ, Chao YK, Wu CY, *et al.* Granulation tissue formation following Dumon airway stenting: The influence of stent diameter. Thorac Cardiovasc Surg 2011;59:163-8.
23. Wood DE, Liu YH, Vallières E, Karmy-Jones R, Mulligan MS. Airway stenting for malignant and benign tracheobronchial stenosis. Ann Thorac Surg 2003;76:167-72.
24. Dumon MC, Dumon JF, Perrin C, Blaive B. Silicone tracheobronchial endoprosthesis. Rev Mal Respir 1999;16 (4 Pt 2):641-51.
25. Hirshoren N, Eliashar R. Wound-healing modulation in upper airway stenosis-Myths and facts. Head Neck 2009;31:111-26.
26. Warner D, Brietzke SE. Mitomycin C and airway surgery: How well does it work? Otolaryngol Head Neck Surg 2008;138:700-9.
27. Simpson CB, James JC. The efficacy of mitomycin-C in the treatment of laryngotracheal stenosis. Laryngoscope 2006;116:1923-5.
28. Roh JL, Lee YW, Park CI. Can mitomycin C really prevent airway stenosis? Laryngoscope 2006;116:440-5.
29. Eliashar R, Gross M, Maly B, Sichel JY. Mitomycin does not prevent laryngotracheal repeat stenosis after endoscopic dilation surgery: An animal study. Laryngoscope 2004;114:743-6.
30. Hueman EM, Simpson CB. Airway complications from topical mitomycin C. Otolaryngol Head Neck Surg 2005;133:831-5.
31. Tanabe K, Serruys PW, Grube E, Smits PC, Selbach G, van der Giessen WJ, *et al.* TAXUS III Trial: In-stent restenosis treated with stent-based delivery of paclitaxel incorporated in a slow-release polymer formulation. Circulation 2003;107:559-64.
32. Wang T, Zhang J, Wang J, Pei YH, Xu M, Zhang X, *et al.* The inhibition effect of paclitaxel on the proliferation of human pulmonary fibroblasts (in Chinese). Chin J Tuberc Respir Dis 2010;33:17-20.

33. Chen N, Zhang J, Xu M, Wang T, Wang YL, Pei YH. The influence of mitomycin C and paclitaxel on the proliferation and apoptosis of human pulmonary fibroblast (in Chinese). Chin J Tuberc Respir Dis 2013;36:655-60.
34. Hartnick CJ, Hartley BE, Lacy PD, Liu J, Bean JA, Willging JP, *et al.* Topical mitomycin application after laryngotracheal reconstruction: A randomized, double-blind, placebo-controlled trial. Arch Otolaryngol Head Neck Surg 2001;127:1260-4.
35. Simpson CB, White S, McGuff HS. Anti-transforming growth factor beta as a treatment for laryngotracheal stenosis in a canine model. Laryngoscope 2008;118:546-51.

Received: 27-11-2014 **Edited by:** Yuan-Yuan Ji
How to cite this article: Qiu XJ, Zhang J, Wang T, Pei YH, Xu M. Nonstent Combination Interventional Therapy for Treatment of Benign Cicatricial Airway Stenosis. Chin Med J 2015;128:2154-61.

Source of Support: This study was supported by grants from the Capital Clinical Application Research (No. Z121107001012128) and Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (No. XMLX201314). **Conflict of Interest:** None declared.