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Effective treatment of post-intubation subglottic stenosis in children with holmium laser therapy and cryotherapy via flexible bronchoscopy

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ABSTRACT

Importance: Post-intubation subglottic stenosis (SGS) in children can be life threatening. Definitive treatment varies and lacks a universally accepted approach.

Objective: We performed a prospective study to assess the safety and feasibility of holmium laser combined with cryotherapy delivered via flexible bronchoscopy for the treatment of post-intubation SGS in children.

Methods: This study involved all patients with post-intubation SGS seen at the Interventional Pulmonology Department of Beijing Children's Hospital between July 2014 and December 2016. Holmium laser treatment and cryotherapy was then performed under flexible bronchoscopy, whose parents refused to accept the alternative standard treatment of tracheotomy and balloon dilation under direct laryngoscopy.

Results: Sixteen patients with post-intubation SGS were included in this study. Ages ranged from 2 months to 12.25 years old. According to the Cotton-Myer grading system, three cases were Grade II, 12 cases were Grade III, and one case was Grade IV. According to the McCaffrey system, eight cases were Stage 1, two cases were Stage 2, and six cases were Stage 3. The average number of procedures was 4.88. Fifteen of the 16 patients achieved clinical cure. One patient achieved clinical improvement. The average treatment course duration was 55.31 days. No severe complications were seen. Post-treatment clinical symptoms, endoscopic findings and quality of life showed marked improvement.

Interpretation: Our study supports the conclusion that holmium laser treatment combined with cryotherapy via flexible bronchoscopy appears to be a safe and feasible treatment for post-intubation SGS in children.

KEYWORDS

Subglottic stenosis, Flexible bronchoscopy, Holmium laser, Cryotherapy, Children

INTRODUCTION

Subglottic stenosis (SGS) is the narrowing of the proximal trachea within the subglottic region. When severe, it can lead to wheezing, stridor, dyspnea, dysphagia, and dysphonia. Endotracheal intubation is the most common cause of SGS. The incidence of post-intubation SGS is 6.63%−17.94%.[1] As compared with open surgery, endoscopic therapies have benefits that include minimal invasiveness, reversibility, shorter operative time, and shorter hospital stay.[2] These endoscopic techniques include balloon dilatation, laser therapy, cryotherapy, argon plasma coagulation, and T-tube and stent placement. For post-intubation SGS in children, there is no universally recommended endoscopic therapy and the various techniques are tailored on a case-by-case basis. Balloon dilatation with adjuvant supportive therapy is the most commonly used method, however, the efficacy is variable with success rates ranging from 40% to 82%.[3]

The holmium laser delivers light energy at a wavelength of 2140 nm. At this wavelength, it is almost completely absorbed by water within 0.4 mm of the laser fiber tip. Holmium laser therapy at time of flexible bronchoscopy is a rarely performed modality. However, in pediatrics, the holmium laser exhibits effective hemostasis, precise ablation, and can be transmitted effectively through the flexible scope. It is the safest laser to use in pediatric interventional treatment. Cryotherapy, on the other hand, is a more common bronchoscopic modality. Cryotherapy is a safe and effective method for the treatment of airway obstruction, with less risk than laser therapy of causing cartilaginous injury.[4] In fact, it can relieve thermal damage caused by laser treatment. We intend to assess the safety and feasibility of holmium laser combined with cryotherapy by flexible bronchoscopy for treatment of post-intubation SGS in children.

METHODS

Patients

This is a prospective study involving all patients of post-intubation SGS seen at the Interventional Pulmonology Department of Beijing Children's Hospital between July 2014 and December 2016, whose parents refused to accept the alternative standard treatment at our hospital of tracheotomy and balloon dilation under direct laryngoscopy. Patients with congenital SGS, tracheomalacia, subglottic trauma, subglottic infection and SGS secondary to autoimmune disease were excluded.

The diagnosis of post-intubation SGS was made by the following criteria: 1) definite medical history of endotracheal intubation; 2) signs and symptoms of dyspnea; 3) multidetector CT and three-dimensional airway reconstruction showing thickening of subglottic tracheal wall without pressure from extratracheal tissue; and 4) microlaryngoscopy or bronchoscopy confirming visible evidence of SGS. The Cotton-Myer[5] and McCaffrey[6] grading systems for SGS were applied. Airway–Dyspnoea–Voice–Swallow (ADVS) Scale,[7] and Activity of Daily Living (ADL) Scale (Supplement 1) were for quality of life assessment.

Procedure

Treatments were performed by the same surgeon with experience in endoscopic procedures in the pediatric airway. The equipment for the procedure included flexible bronchoscopes (BF-P260F with 4.0 mm OD or BF-XP260F with 2.8 mm OD, Olympus Co., Tokyo, Japan), holmium laser therapeutic apparatus (Output Power: 30 W, laser wavelength 2140 nm, Dahua Co., Wuxi, China), cryotherapeutic equipment (cryoprobe with 1.9 mm OD, refrigerant CO_2, ERBE, Germany), and a PTA balloon catheter (4 mm × 15 mm, Medtronic Inc, Italy).

General intravenous anesthesia was performed under the care of a certified anesthesiologist and was adjusted according to patients' general condition and degree of SGS. Under general anesthesia, patients with Cotton-Myer grade I–III stenosis were given mechanical ventilation with laryngeal mask airway (LMA). In patients with Grade IV, tracheotomy was performed before treatment and continuous ventilation was performed through a tracheostomy tube to ensure the safety of the procedure.

Holmium laser was used to remove granulation and scar tissue, generally performed over 1 or 2 sessions. During laser treatment, we lowered the fractional inspiratory oxygen concentration below 40% to avoid airway fire. We set the output power of holmium laser as 8–10 W. Following laser treatment, CO_2 cryotherapy was used on the treated stenotic region to prevent thermal damage.[8,9] Cryotherapy was operated for 20–30 seconds and then rewarmed gradually per cycle. Bronchoscopic re-examination and laser/cryotherapy treatment was performed every 1–2 weeks. For Grade IV, we used balloon dilatation first. The balloon (4 mm × 15 mm) was inflated to 14 atmospheric pressure for 30 seconds and repeated twice.

Adjuvant exogenous inhaled glucocorticoids and antibiotics were given to help prevent restenosis.[10,11]

Follow-up

Follow-up included observation for any worsening respiratory symptoms bronchoscopy for endoscopic visualization. In general, follow-up evaluations were conducted once a week in first month, then at 3 months and 6 months. ADVS scale and ADL were recorded and analyzed.

Outcome measures

We collected clinical data before and after treatment. The severity of SGS, associated symptoms, degree of hypoxia, endoscopic appearance, complication rates, ventilation mode, partial pressure of arterial carbon dioxide ($PaCO_2$), number of procedures, duration of the treatment course, ADVS Scale, and ADL Scale were recorded and analyzed. Clinical cure was defined when a patient exhibited no laryngeal stridor or hypoxia, successful tracheotomy tube decannulation, dramatic improvement in SGS grade, and no development of restenosis on follow-up visits. Clinical improvement was defined as improvement in symptoms and SGS grade, but tracheotomy tube decannulation was unsuccessful or the patient required supplemental intermittent oxygen. Clinical failure was defined as no improvement in symptoms and SGS grade, unsuccessful tracheotomy tube decannulation, and the need for continuous oxygen.[8]

Statistical analysis

The statistical analysis was performed using SPSS 22.0. The differences of $PaCO_2$ before and after treatment were compared by paired samples t test. A value of $P < 0.05$ was considered statistically significant.

Ethics

This study was approved by the Ethics Committee at Beijing Children's Hospital. Informed consent was obtained prior to all procedures.

RESULTS

Sixteen patients with post-intubation SGS were treated with holmium laser and cryotherapy by flexible bronchoscopy. Fifteen patients completed the full treatment course and achieved clinical cure. One patient (with Grade IV stenosis) achieved clinical improvement, but was lost to follow-up (Table 1). There were no clinical failures. There were eight males and eight females, with ages ranging from 2 months to 12.25 years old. Ten patients (62.50%) were between 0–3 years old, four patients (25.00%) were between 3–6 years old, and two patients (12.50%) were greater than 6 years old. Etiologies regarding need for prior intubation included seven cases (43.75%) due to severe pneumonia and respiratory failure, one case (6.25%) due to viral encephalitis, five cases (31.25%) due to surgery, two cases (12.50%) due to a traffic accident injury, and one case (6.25%) due to airway burn. Before the treatment, patients had varying degrees of stridor, retraction, dyspnea, dysarthria, and dysphagia, reflected by the ADVS scale. The ability of daily life decreased in patients reflected by ADL scale (> 3 years old). According to the Cotton-Myer grading system, three cases were Grade II, 12 cases were Grade III, and one

TABLE 1 Patient demographics and the features of treatment

Patient	Sex	Age	Indications for intubation	Cotton -Myer	Mc Caffrey	Airway status	ADVS scale	Procedures	Number of procedures	Duration of treatment (days)	Outcome	Follow-up
1	M	6y2m	Respiratory distress	II	1	Tracheal intubation	$A_2D_4V_4S_4$	Ho*1, Cryo*9	9	98	Cure	No restenosis
2	F	5y6m	Respiratory distress	II	2	-	$A_1D_2V_2S_2$	Ho*2, Cryo*5	5	38	Cure	No restenosis
3	M	5y9m	Respiratory distress	II	3	Tracheal intubation	$A_2D_4V_4S_4$	Cryo*4	4	28	Cure	No restenosis
4	F	8m15d	Craniopharyng-ioma resection	III	1	-	$A_1D_3V_3S_1$	Ho*2, Cryo*9	10	100	Cure	No restenosis
5	M	6m	Head trauma caused by traffic accident	III	1	-	$A_1D_4V_2S_1$	Ho*1	1	18	Cure	No restenosis
6	M	1m27d	Respiratory distress	III	1	NCPAP	$A_1D_4V_3S_4$	Ho*1, Cryo*1	2	14	Cure	No restenosis
7	M	8m20d	Respiratory distress	III	1	Tracheostomy	$A_4D_4V_4S_4$	Ho*1, Cryo*3	3	32	Cure	No restenosis
8	F	5m	Surgery of congenital heart disease	III	1	-	$A_1D_2V_3S_4$	Ho*2, Cryo*3	3	27	Cure	No restenosis
9	M	1y5m	Respiratory distress	III	1	NCPAP	$A_1D_4V_2S_2$	Ho*1, Cryo*2	2	14	Cure	No restenosis
10	F	1y1m	Surgery of congenital heart disease	III	1	-	$A_1D_2V_2S_2$	Ho*1, Cryo*1	1	7	Cure	No restenosis
11	F	8m	Congenital esophageal atresia surgery	III	2	LMA	$A_1D_4V_3S_3$	Ho*2, Cryo*5	5	84	Cures	No restenosis
12	M	2m10d	Respiratory distress	III	3	NCPAP	$A_1D_4V_3S_4$	Ho*1, Cryo*2	2	17	Cure	No restenosis
13	F	1y8m	Burn	III	3	NCPAP	$A_1D_4V_3S_2$	Ho*1, Cryo*9	9	101	Cure	No restenosis
14	F	12y3m	Traffic accident injuries	III	3	-	$A_1D_2V_2S_2$	Ho*2, Cryo*6	6	65	Cure	No restenosis
15	M	4y	Viral encephalitis	III	3	NCPAP	$A_1D_4V_2S_2$	Ho*1, Cryo*7	7	102	Cure	No restenosis
16	F	5y3m	Surgery of congenital heart disease	IV	3	Tracheostomy	$A_4D_4V_4S_4$	Ho*4, Cryo*9, BL*2	9	140	Improvement	Lost to follow-up

AVDS, Airway–Dyspnoea–Voice–Swallow; M, male; F, female; LMA, laryngeal mask airway; Ho, holmium laser; Cryo, cryotherapy; BL, balloon dilatation; NCPAP, nasal continuous positive airway pressure.

case was Grade IV. According to the McCaffrey grading system, eight cases were Stage 1, two cases were Stage 2, and six cases were Stage 3. In all 16 patients, 10 patients (62.5%) needed respiratory support. Among them, two patients ventilated via tracheal intubation, two patients via tracheostomy tube, one patient via LMA and five patients by nasal continuous positive airway pressure (NCPAP).

After the first procedure, respiratory symptoms significantly improved in all patients. Immediately after treatment, all patients exhibited significant improvement in lumen patency on endoscopic view, complete resolution of hypoxia, and improvement in voice quality and swallowing function. At the end of treatment, the ADVS scale reached normal levels in all patients following completion of treatment. They didn't need any respiratory support. Tracheostoma was closed smoothly in patients with tracheostoma assisted ventilation.

Fifteen patients underwent bronchoscopic follow-up after a minimum of 6 months. In all 15 patients, the subglottic lumen remained fully patent without stenosis, granulation, or scar formation, thus revealing satisfactory lasting treatment effect (Figures 1, 2). The ADL scale also showed improvement in all patients on 6-month follow-up (Table 2).

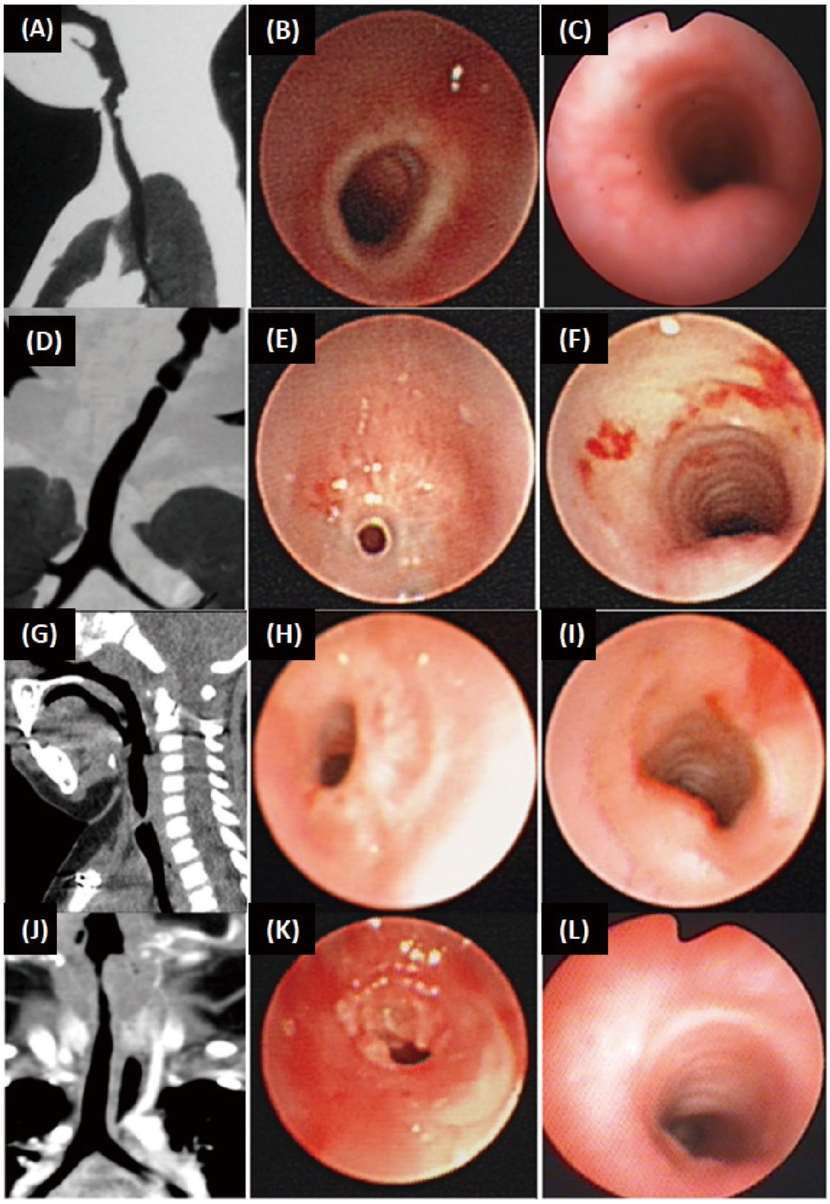

FIGURE 1 SGS with Grade II–III and Stage 1–3. (A) The imaging of SGS with Grade II and Stage 1; (B) SGS with Grade II and Stage 1, before treatment; (C) SGS with Grade II and Stage 1, after treatment; (D) The imaging of SGS with Grade III and Stage 1 (Membranous stenosis); (E) SGS with Grade III and Stage 1 (Membranous stenosis), before treatment; (F) SGS with Grade III and Stage 1 (Membranous stenosis), after treatment; (G) The imaging of SGS with Grade III and Stage 1 (Scar stenosis); (H) SGS with Grade III and Stage 1 (Scar stenosis), before treatment; (I) SGS with Grade III and Stage 1 (scar stenosis), after treatment; (J) The imaging of SGS with Grade III and Stage 3; (K) SGS with Grade III and Stage 3, before treatment; (L) SGS with Grade III and Stage 3, after treatment.
SGS, subglottic stenosis.

$PaCO_2$ was abnormal in seven patients before treatment and showed marked improvement after treatment (P = 0.005) (Table 3).

Among all 16 patients, the average number of individual treating sessions (i.e. holmium laser and cryotherapy) until completion of the treatment course was 4.88 sessions. The average number of laser therapy and cryotherapy were 1.44 and 4.69 times respectively. The time range between individual treatment sessions was between 7 days and 140 days, with an average of 55.31 days.

Complications

During the treatment, there were no significant complications (such as hypoxemia, unexpected bleeding, pneumothorax, pneumomediastinum, or anesthesia complications). A few patients had minimal bleeding when eschars were removed with biopsy forceps after laser, with hemostasis easily achieved after applying a small amount of epinephrine (1:10 000).

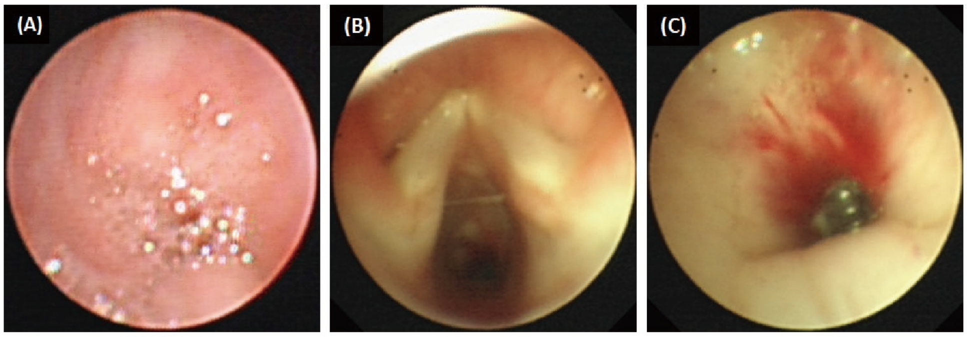

FIGURE 2 SGS with Grade IV and Stage 3. (A) SGS before the treatment with severe stenosis and no perceptible lumen; (B) SGS after the treatment; (C) SGS after the treatment and tracheostomy tube was exposed well. It means that after treatment, the subglottic lumen was markedly enlarged. If the tracheotomy tube was removed, the airway is unobstructed.
SGS, subglottic stenosis.

TABLE 2 Activity of Daily Living (ADL) Scale before and after treatment

Patient number (Age)	Before treatment	After the first treatment	After treatment
4 (6y2m)	0	40	85
5 (12y3m)	80	85	90
14 (4y)	30	65	90
15 (5y9m)	0	75	85
16 (5y6m)	75	75	85

TABLE 3 Comparison of $PaCO_2$ (mmHg) before and after treatment

Patient number (Stenosis grade)	$PaCO_2$ before treatment	$PaCO_2$ after treatment
2 (III,1)	55.0	35.4
4 (II,1)	44.0	38.0
9 (III,3)	67.5	48.1
10 (III,1)	65.0	35.3
12 (III,1)	49.3	41.6
14 (III,3)	46.3	39.4
15 (II,3)	65.5	35.8

$PaCO_2$, partial pressure of carbon dioxide in artery.
$PaCO_2$ showed significant improvement after treatment ($P = 0.005$).

Twenty-four hours post-procedure, one patient experienced labored breathing and hyoxemia. Bronchoscopic examination was immediately performed revealing necrosis and mucus plugging. The obstruction was easily removed bronchoscopically and the patient suffered no lasting complication or restenosis.

DISCUSSION

Post-intubation SGS in children accounts for 90% of acquired SGS. When it occurs, it can have a significant effect on quality of life and even become life threatening. In this study, the majority of patients were under 3 years old (62.50%). The most common etiology regarding the need for prior intubation was respiratory failure in the setting of congenital heart disease and congenital esophageal atresia surgery (68.75%).

We hypothesize that younger age patients are more susceptible to post-intubation SGS due to smaller subglottic lumen diameters, looser basal mucosal tissue, and more abundant lymphatic and vascular tissue. In this setting, every 1 mm reduction in lumen diameter can result in 60% reduction of the effective ventilatory area, thus greatly increasing airway resistance.[12]

Classification on the severity of SGS plays an important role in providing prognostic information and guide treatment decision making. As such, patients in our study were symptomatic from their stenosis and required urgent treatment. The majority of our patients were Cotton-Myer Grade III (81.25%) and McCaffrey Stage 2 or above (50%). ADVS and ADL scales revealed that the majority of our patients suffered from dyspnea, dyslalia, and dysphagia prior to treatment. Ten patients (62.5%) needed respiratory support with mechanical ventilation before treatment.

In all 16 patients, signs and symptoms immediately improved following treatment with holmium laser and cryotherapy (i.e. significant improvement in endoscopic lumen diameter, respiratory symptoms, hypoxemia, voice quality, and swallowing function).

Fifteen patients achieved clinical cure. Follow-up endoscopy after a minimum of 6 months revealed no restenosis. This therapeutic effect and duration appears superior to prior published treatments.[3,8,13,14] For example, balloon dilatation combined with cryotherapy has been performed,[8,9] but did not achieve a satisfactory treatment effect for SGS.[15]

In several previous studies, tracheotomy was a precondition for the treatment of SGS,[16,17] however, tracheotomy itself confers certain risk. These risks include infection and granulation around the tracheostomy tube which can further complicate the treatment course of the SGS. In addition, tracheostomy tube placement can lead to an enormous psychological trauma in children. In this study, patients with SGS Grade I-III underwent treatment safely without the need for tracheostomy.

Furthermore, long segment SGS has been a difficult clinical problem.[18] In our study, SGS with length ≥ 1cm accounted for 50%, and in all cases, satisfactory therapeutic effect was achieved with holmium laser and cryotherapy.

Holmium laser has a cutting ability similar to the CO_2 laser and a coagulation ability similar to the Nd: YAG laser. As such, it can remove granulation and scar tissue effectively. Application of the holmium laser delivered via flexible endoscopy is precise and effective. It is widely used in fields of otolaryngology,[19] urology[20] and gastroenterology.[21] Fong et al[22] reported the first application of holmium laser for disorders of the pediatric airway. An 8-year experience of holmium laser ablation via bronchoscopy confirmed safety and feasibility for benign and malignant tracheobronchial obstructions.[23] Since the airway diameter in children is small and the effective operation area is restricted, the holmium laser was felt to be a good alternative treatment method. When compared with balloon dilation, the holmium laser may be superior for removing granulation tissue and scar formation by causing destruction of vasculature and blood flow to the diseased region.

In response to concerns that laser destruction could itself lead to additional granulation tissue formation, laser treatment can be followed by cryotherapy to prevent granulation regeneration and maintain lumen diameter.[24] The pathophysiology is felt to arise from the effect of cryotherapy on further reducing blood supply, inhibiting hyperplasia of granulation, and increasing the synthesis of collagen. Cryotherapy promotes cicatricial fibroblast differentiation into normal fibroblasts so as to reduce scar and granulation tissue hyperplasia.[25,26] Zhang et al[27] showed that cryotherapy has good curative effect on the treatment of SGS and is effective in preventing restenosis. Early and repeated intervention may be one reason for the high success rate in children.[14]

In our study, treatment was safe with no serious complications (both during and after treating sessions). One patient experienced transient labored breathing and hypoxemia 24 hours after the procedure, but no lasting complication. This was felt to arise from necrotic epithelium obstructing the airway. From our experience, the aftereffect of cryotherapy may be the contributor to the complication in this case. Therefore, within the first 72 hours post-cryotherapy, we recommend close attention and monitoring of patients' respiratory status.

Success of combined holmium laser-cryotherapy treatment can be confounded by other factors, including the experience of the surgeon as well as the patients' adherence to routine and continued intervention and care. In our study, the surgeon performing these procedures had significant experience with pediatric endoscopic techniques and the patients exhibited good compliance to their regular follow-up treatments.

Our study has some limitations. These limitations include the small sample size which has an effect on the power of our conclusions. In addition, because the one patient with SGS Grade IV was lost to follow-up, we have limited understanding on the longstanding effect of our treatment on SGS Grade IV.

Our study supports the conclusion that holmium laser treatment combined with cryotherapy by flexible bronchoscopy appears to be a safe and feasible treatment for post-intubation SGS in children. This includes SGS with lengths ≥ 1cm. Furthermore, this therapeutic technique can be considered a viable alternative option when performed by a practitioner with appropriate training and supervision.

CONFLICT OF INTEREST

The authors have declared no conflicts of interest. All authors have read the manuscript and agree with the submission.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the supporting information tab for this article.

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