

Surgical treatments for post-intubation laryngotracheal stenosis in patients with central nervous system injuries

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Abstract

Post-intubation laryngotracheal stenosis is a complication commonly encountered in patients with central nervous system (CNS) injuries, often preventing decannulation. To date, no data is available in the literature focusing on this issue. Our objective was to describe surgical treatments for laryngotracheal stenosis and discuss factors associated with successful decannulation in this group of patients.

Medical records of patients with CNS injury who received tracheal surgeries at our institution between 2009 and 2016 were retrospectively collected and analyzed.

Data on 124 surgeries in 62 patients with CNS injury were collected. The total complication rate was 20.9% with no surgical mortality. The decannulation success rate was 85.5%. Argon laser surgeries (48), diode laser surgeries (22), tracheal resection and reconstructions (R&R) (9), and tracheal T-tube placements (67) were performed. The average times from the first bronchoscopy check up to surgery and surgery to decannulation were 0.7 and 8.2 months, accordingly. The mean post-decannulation follow-up time was 13.5 months. A shift from the use of rigid bronchoscopy in the initial surgeries to laryngeal mask in the latter surgeries yielded an average decrease of 3 days in hospital length of stay (LOS). A change from initial rigid bronchoscopic core out procedures and argon laser to interventional flexible bronchoscopic resections with diode laser also decreased LOS significantly.

Surgical treatments for patients with CNS injury and laryngotracheal stenosis can be safely performed with low mortality, acceptable complications, and a high decannulation success rate. The majority of patients with laryngotracheal stenosis can be managed with laser endoscopic surgeries, though tracheal R&R might still be required in selected cases. The use of laryngeal mask to secure the airway and diode laser in the intra-luminal resections improved the surgical outcome and was therefore recommended for these patients suffering from post-intubation laryngotracheal stenosis.

Abbreviations: CNS = central nervous system, CVA = cerebrovascular accidents, LOS = length of stay, P-A = penetration-aspiration, R&R = resection and reconstructions.

Keywords: central nervous system, laryngotracheal stenosis, lasers, surgical endoscopy

1. Introduction

Cerebrovascular accidents (CVA) and trauma are leading causes of death worldwide,^[1] including Taiwan.^[2] The central nervous system (CNS), consisting of the brain and the spinal cord, performs vital body functions such as respiration, swallowing,

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and speech. Impairment of the CNS as a result of either CVA or head and spine injuries often leads to endotracheal intubation and tracheostomy. Tracheostomy is required in 10% of patients with CNS injury and can be as high as 50% to 70% in patients with a Glasgow Coma Scale $< 9.^{[3]}$

After stabilization of the initial acute stage of CNS injury, one of the most important rehabilitation goals is to wean the patients from tracheostomy. However, due to excessive saliva, hypertonia, and brain hypoxia, it is a major challenge to achieve decannulation in this group of patients.^[4] In addition to the CNS dysfunctions, tracheal complications from prolonged endotracheal intubation and tracheostomy might also lead to tracheostomy dependence. Post-intubation airway stenosis has been reported in 15% of patients with CNS injury.^[3] The surgical management of these complications is critical for successful decannulation. However, to our knowledge no available reports in the medical literature focus on this issue. In this study, we present our experience in the surgical management of laryngotracheal stenosis in patients with CNS injury.

2. Materials and methods

Consecutive patients who underwent tracheal surgeries other than a tracheostomy between 2009 and 2016 in a tertiary medical center were enrolled. All details were recorded at the time of the procedures, and the charts were reviewed retrospectively. This study was approved by the organization's Institutional Review Board.

2.1. Pre-operative evaluation and surgical approaches

The indications for tracheal surgeries were:

- 1) patients experienced dyspnea and stridor,
- 2) patients failed corking, and
- patients presented with a tracheal obstruction > 50% of the cross-sectional area (Cotton's classification for laryngotracheal stenosis of grade II or more).^[5,6]

Special attention was paid to note saliva pooling or choking under bronchoscope examinations. Patients were graded for severity of choking according to the 8-Point Penetration-Aspiration (P-A) Scale.^[7] We further simplified the grading system into no (P-A score 1–2), mild (P-A score 3–4), moderate (P-A score 5–6), and severe (P-A score 7–8) choking. Patients who suffered from a P-A score of 8 were excluded from tracheal surgeries as the intention of the surgeries was to keep the airway patent and to successfully decannulate the artificial airway.

Computed tomography (CT) of the neck was routinely used for pre-operative evaluation to accurately assess the diameter and anatomical location of the trachea and lesions.^[8]

The concomitant vocal cord granuloma or fusion was resected/ opened with a flexible bronchoscope using argon or diode laser, and sometimes a transcord T-tube was placed.

The treatment of choice for subglottic and tracheal stenosis was tracheal resection and reconstruction (R&R) when the following criteria were met: patients had little or no swallowing/ choking problem, the stenotic segment did not exceed more than half of the length of the trachea, the neck was long enough, the patient was not obese, and the patient could accept 7 days of neck flexion and chin fixation stitches.

The Montgomery Safe-T-Tube (Boston Medical Products, MA) was placed using an interventional bronchoscope approach. Before 2013, the rigid bronchoscope was used to core out obstructing lesions of the trachea followed by coagulation with the argon laser. After the introduction of the powerful diode laser (5 mW 635–660nm, AngioDynamics, NY) with a flexible bronchoscope, we switched to utilizing the laryngeal mask as a ventilation route, which minimizes trauma to the vocal cords. We used an upper gastrointestinal endoscope to manipulate the airway of patients with C-spine injuries as the rigid bronchoscope was contraindicated, and ventilation was through a tracheostomy tube. The T-tube removal was planned for 6 months after the surgery.

Montgomery Tracheal Cannula (Boston Medical Products, MA) was used to maintain the stoma as a bridge to decannulation when no more stenosis was observed. When stenosis was still present, the airway would be augmented with a T-tube again. The trachea was observed for one more month, and the cannula was removed if no further airway stenosis was noted. The treatment course was thus completed. The patients were followed up for airway patency with bronchoscopy as needed.

2.2. Data analyses

The demographics, comorbidities, CNS injuries, bronchoscopic findings, CT findings, operative methods, and follow up data were collected. The primary outcome was the successful decannulation of the patients. The secondary outcomes were the complications of the tracheal surgeries and the length of hospital stay (LOS). The statistics were performed with SPSS 21 (Armonk, NY: IBM Corp). Analyses of data included frequency, range, mean, median, SD, χ^2 test or log-rank test for categorical variants, and Student *t* test for continuous variants. The Wilcoxon signed rank test, Mann-Whitney *U* test, or Kruskal-Wallis test was used to test the LOS. The multivariate analysis was initially performed with linear regression and ANOVA. However, when it failed to detect any significant results, we created 8 subgroups by the surgeries according to rigid bronchoscope/laryngeal mask, tracheal T-tube/tracheal cannula, and argon laser/diode laser, and then tested with ANOVA.

3. Results

3.1. Patients

From 2009 to 2016, data for 83 consecutive patients who underwent tracheal surgeries other than a tracheostomy were collected. Twenty-one were excluded because they did not have CNS injuries (Table 1). The gender was equally distributed. The mean age was 45.8 ± 18.9 (range 9–80) years. The body height, weight, and BMI were around the population averages. For patients with brain infarction and hemorrhage, 75.0% and 90.0% had hypertension respectively.

Brain injuries were noted in 55 (88.7%) patients, C-spine injuries in 8 (12.9%), and one had both (Table 1). Trauma occurred in 23 of the brain-injured patients and in all 8 C-spine patients constituting 50%, while brain hemorrhage occurred in 20 and infarction in 8. Patients with C-spine trauma had C1 to C6 injuries and everyone had a C3 injury.

Table 1

Types of CNS injuries in patients who rece	eived tracheal surgeries.
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	n (62)	%
Brain Events	55	88.7
Infarction	8	12.9
Hemorrhage	20	32.3
Aneurysm	5	8.1
Hypoxia	5	8.1
Arteriovenous malformaion	4	6.5
Tumor	2	3.2
Trauma	23	37.1
Brain	55	88.7
Subdural hematoma	10	16.1
Subarachnoid hemorrhage	24	37.8
Intracranial hemorrhage	22	35.5
Intraventricular hemorrhage	12	16.4
Hydrocephalus	23	37.1
Cerebrum	38	61.3
Frontal	21	33.9
Parietal	14	22.6
Temporal	20	32.3
Occipital	4	6.5
Basal Ganglion	16	25.8
Brainstem	10	16.1
Midbrain	3	4.8
Pons	8	12.9
Medulla	2	3.2
Cerebellum	3	4.8
C-spine (C3)*	8	12.9

All of the C-spine injuries were associated with trauma

Table 2	
Milestone ti	mes of patients with CNS injury who received tracheal
surgeries.	

Start	End	Median	Range
Tracheostomy or Stenosis	Bronchoscopy	3.6	0, 48.7
Tracheostomy or Stenosis	Surgery	4.7	1.9, 56.5
Bronchoscopy	Surgery	0.7	0, 30.9
Surgery	Decannulation	8.2	0, 23.0
Decannulation	Follow-up	13.5	0.13, 95.5

unit (months).

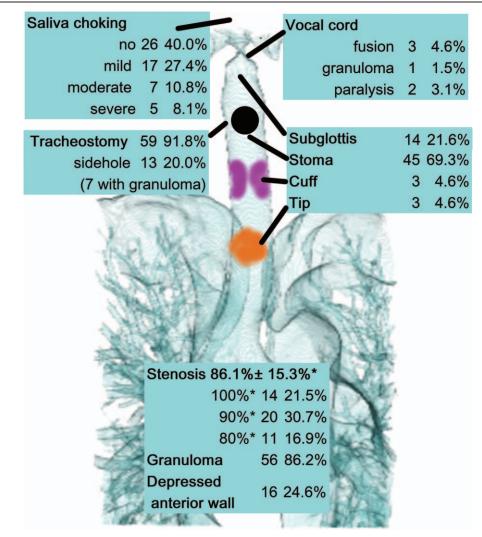
Only 14.5% of the tracheostomies were performed at our hospital. The median time of tracheostomy to 1^{st} bronchoscopy examination was 3.6 (range 0–48.7) months (Table 2). There were 6 vocal cord and 14 subglottic lesions (Fig. 1). Stenosis of more than 70% of the tracheal cross-section (Cotton's classification of grade III or more)^{15–61} was diagnosed in 45 patients. There were 56 (86.2%) with tracheal granulomas. Most of the stenoses were at the stoma level (45, 69.3%). Fifty-nine (91.8%) patients presented with a tracheostomy tube, 13 of which had a side hole, with 7 of them having a granuloma at the side hole.

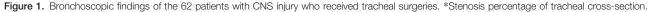
Only 12 patients had moderate or severe choking on saliva when initially surveyed but they improved before surgery.

3.2. Surgeries

The median time from the tracheostomy and first bronchoscopy survey to the tracheal surgery was 4.7 and 0.7 months, respectively (Table 2). There were 124 surgeries performed in 62 patients (Table 3). Patients received 2 operations on average; the number of patients who received one, two, three, and four operations were 19, 27, 13, and 3 correspondingly.

Four patients had vocal cord surgeries, 9 patients received R&R, and 50 had tracheal T-tube placements. The subglottic lesions were treated with one R&R, 13 T-tubes with 6 transcord, and 3 combined with vocal cord surgeries. Three patients who had granulomas at the tip of the tracheostomy tube were treated with granuloma resection and the placement of an extended-length tracheostomy tube as a stent. Vocal cord surgeries were performed in 1 R&R and 3 T-tube patients. Forty-three T-tube patients received a second surgery with tracheal cannula implantation in the majority, while the rest received T-tube





Types of tracheal surgeries for CNS injury patients.

		1st		2nd		3rd	
Surgeries		n	%	n	%	n	%
Operation	Tracheal resection & reconstruction	9 (1*)	14.5				
Methods	Tracheal T-tube	50 (13*)	80.5	15 (4 [*])	34.9	2	12.5
	Long tracheostomy	3	4.8				
	Vocal cord	4 (3*)	6.5	1	2.3		
	Tracheal cannula			26 (9*)	60.5	10 (2*)	62.5
	Close fistula			1	2.3	4	25
	Total	62	100	43	100	16	100
Route	Rigid bronchoscope	36 (31 [†] ,6 [*])	67.9	18 (7 [†] ,4 [*])	43.9	2 (1 [†])	16.7
	Laryngeal mask	14 [†] (7 [*])	26.4	23 (6 ⁺ ,8 [*])	56.1	10 (1 ^{+,2} *)	83.3
	UGI-scope	3 (2 ⁺ ,1 [*])	5.6				
	Total	53	100	41	100	12	100
Resection	Argon Laser	33 (6*)	68.7	10 (2*)	62.5	5	55.6
tool	Diode Laser	13 (7*)	27.1	6 (4*)	37.5	3	33.3
	Microdebrider	2	4.2			1	11.1
	Total	48	100	16		9	100
T-tube	Regular	42 (7*)	84	11 (2*)		2	100
type	Transcord	8 (6*)	16	4 (2*)			
Trimming of T-tube	14	28	3	33.3			

* Surgeries for subglottic stenosis, n = 14.

[†] The route used for tracheal T-tube surgery.

replacement. The cannula implantation was also the most frequent 3rd surgery.

The rigid bronchoscope was used in 56 surgeries to secure the airway, including 39 T-tubes, 12 cannulas, 3 R&R, and 2 extended-length tracheostomy tubes (Table 3). The laryngeal mask was used in 47 surgeries, including 26 tracheal cannulas, and 21 T-tubes. Argon laser was used in 48 granuloma resection surgeries and diode laser in 22. Microdebrider was applied in 2.^[9]

There were 12 13 mm trans-vocal-cord T-tubes with tapered tips among the 67 T-tubes, which were used in patients with vocal cord fusion, subglottic stenosis, or post-T-tube tip granuloma (Table 3). The most frequently used T-tube was the 12 mm. T-tubes were trimmed to size in 17 placement surgeries.

3.3. Outcomes

Among the 62 patients, 4 moved to another city after surgery and were lost to follow up and 10 were extubated then lost to follow up. The median time of follow up was 13.5 months from decannulation (Table 2).

Table 4				
Causes of decannulation failure.				
	n	%		
Aspiration pneumonia	3	33.3		
Vocal cord paralysis	2	22.2		
Tracheal restenosis	3	33.3		
CNS disease progression	2	22.2		
Brain Injury	8	14.5*		
C-spine Injury	2	25*		
Complication (+/-) [†]	2 /7	10.5 /16.3		
Subglottic [‡]	5	55.5		
Total	9	100		

* Of brain and C-spine injuries.

 $^{\dagger} P = .43.$

*1 restenosis, 1 vocal cord paralysis.

The overall success rate for patients to be free from any artificial airway was 85.5%. The median time of decannulation from the first operation was 8.2 months (Table 2). All of the R&R patients were extubated successfully. Nine (18%) T-tube patients failed extubation and went back to tracheostomy (Table 4). Three of them, all with choking problems, had aspiration pneumonia. Bilateral vocal cord paralysis was not detected preoperatively in 2 patients. Tracheal restenosis with granuloma or partial tracheal focal malacia occurred in 3. The CNS condition worsened with severe seizures (1 with aspiration pneumonia) in 2 patients. Of these 9 patients, 5 had subglottic stenosis.

There was no surgery related or airway stenosis related mortality. The complication rates were 27.2%, 14.0%, and 12.5% for 1st, 2nd, and 3rd operation, accordingly (Fig. 2). There were 5 complications among the 9 R&R patients. An anastomosis dehiscence occurred after a patient involuntarily shook his head, and an ensuing surgical repair was required. Two patients had anastomosis restenosis- one was treated with balloon dilatation and the other was closely observed. A patient experienced sputum impaction with dyspnea and was treated with bronchoscopic removal. Fourteen (20.9%) of the T-tube surgeries had a complication, most of which were related to the development of tip granulomas. Two patients had poor T-tube hygiene with sticky sputum impaction that required removal and cleaning of the tubes. Two patients with trans-vocal-cord T-tubes had subglottic stenosis and could not tolerate the T-tubes. The tubes were changed to tracheostomy tubes; one of the patients had a C2-7 fracture. The distal end of the trans-vocal-cord T-tube was too long and the left lung subsequently collapsed in a 155 cm tall female, therefore it was necessary to trim the T-tube. Due to abrasion of the tracheal epithelium by the T-tube, surgical intervention was needed in a patient when 'late bleeding' was noted. Four patients (11.1%) with a tracheal cannula had complications, 2 with stoma granulomas were treated with resection, one had cannula dislodgement, and one had aspiration pneumonia.

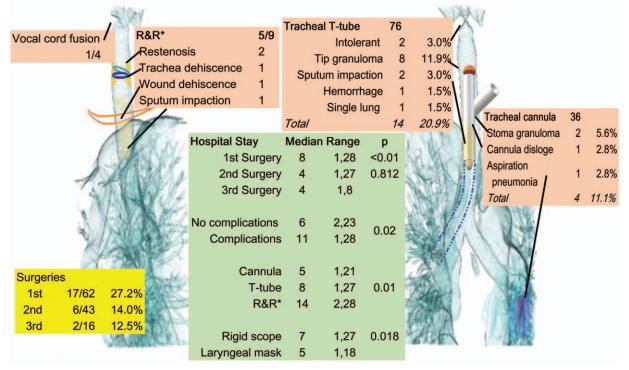


Figure 2. Outcomes of the tracheal surgeries for patients with CNS injury. The yellow and orange squares show complication numbers and rates for different surgeries. The green square shows the length of hospital stay. *R&R tracheal resection and reconstruction.

The hospital stay was 14, 8, and 5 days for tracheal R&R, Ttube, and cannula, accordingly with statistically significant differences (Fig. 2). The latter operations required shorter hospital stays than the earlier ones. Considering the route of airway maintenance, the hospital stays decreased significantly from 7 to 4 days for rigid bronchoscope and laryngeal mask, respectively (P=.001). Similarly, changing the argon laser to diode laser also decreased hospital stays significantly (P=.009). After grouping the surgeries into 8 categories, the combination of laryngeal mask and diode laser decreased LOS to 5.6 and 4.2 days for tracheal T-tube and tracheal cannula, respectively.

4. Discussion

The weaning from tracheal implantation is a big milestone for patients with CNS injuries, hence the importance of this study to determine the factors involved in successful decannulation. To our knowledge, no previous investigation has been published on tracheal surgeries pertaining to this group of patients.

Our patients were mostly victims of trauma and CVA, especially hemorrhagic instead of ischemic strokes with hypertension.^[10] This may be attributed to the need for tracheostomy and poor GCS scores in these patients.^[3] Although the brain stem comprises only 2% of the total brain volume,^[11] 16.1% of our patients had brain stem injuries (Table 1), demonstrating the important function of the respiratory and swallowing center the brain stem. Similarly, all C-spine patients enrolled had a C3 injury, which is compatible with the location and respiratory function of the phrenic nerve.

A previous study on laryngotracheal stenosis in patients with neurological disease concluded that there was no correlation between the duration of intubation before the occurrence of stenosis.^[12] Other studies on different patient populations showed that with every additional 5 days of intubation there was an increase of 50.3% chance of developing subglottic stenosis in the pediatric population,^[13] and a duration of 54.5 days of intubation was associated with the development of tracheal stenosis in adults with different underlying diseases.^[14] Our study revealed a median duration of 3.6 (range 1.9–56.5) months from tracheostomy to the first bronchoscopy diagnosis of laryngotracheal stenosis (Table 2). The findings were varied because investigational criteria and patient populations were different. However, our results suggested more complex issues involved with the care of the airway in patients suffering from central nervous system injuries.

In our investigation, patients received tracheal surgeries when they had stenosis of more than 50% of the tracheal diameter (Cotton's grade II or more).^[5–6] In previous studies, R&R was the treatment of choice for most benign tracheal stenoses,.^[15–16] However, patients with CNS injuries might not be able to accept 7 days of neck flexion even with chin-stitches. In addition, their choking condition is a relative contraindication for surgery. Though our complication rate was as high as 55%, which was much higher than that reported by Dr Grillo for different patient groups (31.5%),^[16] they were all manageable without lifethreatening issues. In our series, the majority of patients received laser endoscopic tracheal surgeries for laryngotracheal stenosis, which has the advantage of using a flexible endoscopic approach which is especially valuable in patients with C-spine injuries and yields a high decannulation success rate.

All of our patients were free from any tracheal implants after surgery. The most troublesome case had a restenosis that we treated successfully with dilatation.^[17] A tracheal cross-section of 50% patency, Cotton's grade I stenosis, was enough for most of the patients to perform their rehabilitation and daily activities. Tracheal R&R was still the preferred choice for a few selected patients. For patients deemed unsuitable for R&R, interventional laser bronchoscopy with a trachea stent offered a minimallyinvasive alternative.

Calluccio et al reported good endoscopic treatment results for benign tracheal stenosis with failure rates of 4% in all the cases and 31% for complex patients; with an average of 2.07 and 3.27 surgeries for simple and complex cases.^[18] Our patients received 2.0 surgeries on average including a short-term tracheal cannula. Puma et al. had successful decannulation in 10 out of 37 patients treated with a silicon stent for cicatricial tracheal stenosis.^[19] Forty-one of our 50 (82%) T-tube patients achieved successful decannulation. The success rate of decannulation was compatible with those reported by Calluccio et al and Puma et al in other groups of patients.^[18–19]

No surgical mortality was reported in this study. The strategy of using a tracheal cannula as a bridge for one month, instead of direct T-tube removal, might play a role in protecting the airway. When tracheal restenosis or aspiration occurred, the cork of the cannula could be removed for ventilation. Within this critical month of close observation, extubation could only be safely performed when restenosis or choking did not occur.

In this investigation, the most frequent complication of the T-tube surgery was restenosis with T-tube tip granuloma (Fig. 2); some occurred in as few as 3 days after the operation. As a safety precaution, patients were discharged only after they could tolerate corking. The tip granuloma might have been caused by irritation of the tip end against the trachea wall due to a poor T-tube angle, especially when the original tracheostomy channel was not perpendicular to the trachea. We overcame this problem by moving the stoma location caudally.^[20] Tip granuloma could also be due to the tip end abutting the conus elasticus in subglottic stenosis. Some reports similarly attributed the development of tip granulation tissue to abrasion of the T-tube tip against the tracheal mucosa during talking and swallowing movements.^[21-22] In such cases, though uncomfortable, a trans-vocal cord T-tube is unavoidable. Interestingly, Schmal et al reported the occurrence of granulation tissue in as high as 74% of Montgomery T-tubes, all of which were associated with infection instead of foreign body reaction, and predominantly with Staphylococcus aureus and Pseudomonas aeruginosa.^[23] The same 2 infective organisms were also found in other airway stents to be the causative agents for the development of airway granulation.^[24] Therefore, extra considerations are mandatory in the postoperative care to ameliorate both tracheal irritation and infection in order to achieve successful outcome for the treatment of laryngotracheal stenosis.

The airway was maintained with a rigid bronchoscope in the initial cases. After establishing the airway and maintaining it, core-out procedures were performed. Hemostasis and minor debridement were achieved by the argon laser. Nevertheless, the surgical procedure was highly technique-dependent and posed potential risks for vocal cord trauma and edema.^[12,17] In the latter cases, the diode laser delivered by a flexible bronchoscope was introduced, and we switched to a laryngeal mask to maintain the airway. With the use of the laryngeal mask, the ventilation route could be secured with less trauma and monitored under direct vision with the bronchoscope. Not only did the laryngeal mask offer a safer route of airway maintenance, both the bronchoscope and diode laser could also be passed through with greater ease and yielded ample space for manipulation. There was no conversion to an endotracheal tube or a rigid bronchoscope.

All of the patients could tolerate corking on the day of or the day after surgery and were discharged soon after. The length of hospital stays subsequently decreased significantly (Fig. 2).

The application of the diode laser via a rigid or flexible endoscope has been reported in neurosurgery,^[25] otology,^[26] and urology.^[27] Diode laser has the advantages of deeper tissue penetration and more precision offered by the contact laser. Compared to the argon laser, the effects of which are more superficial, the diode laser can be used more efficiently to resect the stenotic lesions, as illustrated by the improved outcome in our study. Galluccio et al also used the more powerful neodymiumdoped yttrium aluminum garnet laser for their study, which yielded good long-term results.^[18] From our experience, we would therefore recommend the use of diode laser over the argon or carbon dioxide laser in the treatment of laryngotracheal stenosis as it offers both deeper tissue penetration and improved precision.

Not surprisingly, swallowing dysfunction was observed in approximately half of the patients with CNS injury,^[28–29] and saliva pooling and choking were noted in 60% of patients who were selected to receive tracheal surgeries in this study. Tracheostomy was performed due to this complication, which can make decannulation very difficult. Most of these patients resumed swallowing rehabilitation and kept their tracheostomy. Only 12 patients with moderate to severe choking were trained well enough to receive T-tube surgery. One of the 5 and 2 of the 7 patients with severe and moderate saliva pooling failed decannulation. Of the 3 patients who failed decannulation due to aspiration pneumonia, 2 had moderate choking that did not improve after the T-tube surgery. Choking, therefore, was a very important factor that prevented patients with CNS injury from achieving decannulation, and aggressive swallowing rehabilitation should be mandated.

The patients with subglottic stenosis also had treatment limitations. Tracheal R&R remained the standard choice of treatment.^[30] However, due to the limitations posed by CNS injuries, only 1 of 14 patients received R&R. We used a transvocal cord T-tube in 6 of the patients who had stenosis very close to the vocal cord. Five patients still failed decannulation and composed more than half of the failed cases. Therapeutic endoscopic treatment has been reported as a successful approach in 66% of simple cases.^[31] Our results were similar (64.3%). We need better approaches for this group of patients.

5. Conclusions

Laryngotracheal stenosis in patients with CNS injuries can be safely managed surgically with improved morbidity rates and without surgical mortality. The usage of laryngeal mask to maintain the airway and diode laser with a flexible bronchoscope to perform the resection improved the surgical efficiency and shortened hospital stays; the operation is especially recommended for patients with C-spine injuries. This is the first report to focus specifically on surgical treatments for tracheal stenosis in patients with CNS injuries.

Author contributions

Conceptualization: Frank Cheau-Feng Lin. Data curation: Stella Chin-Shaw Tsai, Frank Cheau-Feng Lin. Formal analysis: Stella Chin-Shaw Tsai. Investigation: Stella Chin-Shaw Tsai, Frank Cheau-Feng Lin. Writing – original draft: Frank Cheau-Feng Lin. Writing – review & editing: Stella Chin-Shaw Tsai. Frank Cheau-Feng Lin orcid: 0000-0001-5301-2345.

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