A Preliminary Study on the Effect of Botulinum Toxin in the Prevention of Glottic Web Reformation

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Abstract

Introduction: The risk of recurrence is associated with all currently available surgical modalities for the treatment of congenital anterior glottic webs. Physical separation of the raw mucosal surfaces is essential until complete healing. Botulinum toxin injected into the thyroarytenoid muscle of a vocal fold for achieving separation between healing tissues has successfully prevented further synechiae formation.

Aim: To compare and evaluate the effect of intraoperative botulinum toxin injection for prevention of recurrence in endoscopically treated congenital anterior glottic webs.

Materials and methods: A prospective comparative analytical study of six cases was carried out over 1 year. Cases with a thin Cohen's grade I or II congenital anterior glottic web were included and randomized into two groups. Group I underwent endoscopic cold knife web division with keel placement, and Group II subjects additionally received botulinum toxin injection intraoperatively. Patients were followed up after 6 weeks and the degree of residual/recurrent web was recorded.

Results: The preoperative mean percentage of anterior glottic web in both groups was 46.67 ± 2.36. The postoperative mean percentage of anterior glottic web was 26.67 ± 6.24 in Group I and 13.33 ± 4.71 in Group II. The mean percentage of the length of the glottis involved by web improved in both groups postoperatively, i.e., by 20.0 in Group I ($p = 0.00065$; significant) and by 33.34 in Group II ($p = 0.0004$; significant). The difference in improvement between both the groups postoperatively was 13.34% ($p = 0.0417$; significant).

Conclusion: Botulinum toxin due to its paralytic effect on the thyroarytenoid muscle decreases web reformation and can therefore be used along with the established techniques in the treatment of anterior glottic webs.

Keywords: Anterior glottic web, Botulinum toxin, Keel.

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Introduction

First reported in 1882 by Fleischmann during an autopsy study of an infant,[1] congenital laryngeal web is a rare malformation, occurring in 1 in 10,000 live births and <5% of all congenital laryngeal anomalies.[2] Incomplete recanalization of the laryngotracheal lumen during the third month of gestation results in different degrees of laryngeal stenosis.[3] The most common site of involvement is the anterior glottis, frequently associated with infra-/subglottic extension.[4]

Surgical intervention is indicated in a web causing airway obstruction and/or an abnormality of the voice, and the common goal of intervention being restoration of airway patency and improvement of voice quality.[4,5] Several surgical modalities have been attempted, which include endoscopic and external approach techniques. Endoscopically, this entails web incision with cold instruments or laser, with/without mitomycin-C application, and silastic keel insertion in the anterior commissure. Externally, options include an anterior cricothyrotomy with silastic keel placement or laryngotracheal reconstruction (anterior expansion) in case of a thick web.[6] However, none of these are infallible and a risk of web reformation exists.[1] Thus, it is imperative to employ methods that ensure adequate physical separation of the raw mucosal surfaces until healing is complete.[4] Single modality treatment of an anterior web hence remains unsatisfactory and its management an ongoing challenge.[7]

Limited studies on the use of botulinum toxin in the prevention of posterior glottic synechiae have shown that botulinum toxin injected into the interarytenoid and thyroarytenoid muscles

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facilitated separation between healing tissues, thereby ensuring the prevention of further synechiae formation.[8]

This study was thus undertaken with the objective of comparing and evaluating the efficacy of intraoperative botulinum toxin injection in the prevention of recurrence in endoscopically treated congenital anterior glottic webs.

Materials and Methods

A prospective comparative analytical study of six cases was carried out over 1 year in 2019. All consenting cases who presented with the complaint of a weak voice since birth, without dyspnea, stridor, or any other comorbidity, diagnosed with a thin congenital anterior glottic web (according to Cohen's staging system) and undergoing endoscopic web division, were included in this study. Those with subglottic extension of web, history of laryngeal trauma, other

laryngeal pathology, undergoing laryngofissure, or attrition to follow-up were excluded.

Outpatient laryngoscopic confirmation of the diagnosis was performed. Surgical intervention was performed in all cases by the same surgeon (first author) as follows: under general anesthesia, with a microlaryngeal tube *in situ*, the larynx was exposed with a Kantor Berci videolaryngoscope. Of the six cases, only case number 4 required a tracheostomy due to difficult instrumentation with the endotracheal tube *in situ* owing to the age of the patient, i.e., 2 years. Palpation of the web for assessment and confirmation of its thickness and inferior extension was carried out using blunt instrumentation. Following its infiltration with 2% lidocaine plus adrenaline, the web was divided from posterior to anterior, upto the anterior commissure.

An appropriately sized keel was fashioned from a 0.5-mm thick silastic sheet and secured with Prolene 4.0 sutures cannulated through two 21 G spinal needles passed from the skin into the laryngeal lumen through the thyroid cartilage in the midline. The keel was fixed in position such that its superior edge was placed just above the vocal fold to separate its raw margins. The sutures were secured over a silastic bolster on the anterior neck skin.

Cases were then randomized into two groups. Patients in Group I did not receive intraoperative botulinum toxin A injection (control group), while patients in Group II received 2.5 MU botulinum toxin A injection intraoperatively into each thyroarytenoid muscle bilaterally (experimental group). The keel remained *in situ* for 2 weeks, after which endoscopic removal of the keel was performed along with topical mitomycin-C application. At the end of 6 weeks, postoperative fiberoptic laryngoscopic reassessment was performed and the degree of residual/recurrent web was recorded as the percentage of glottic length involved by the web.

Descriptive and inferential statistical analysis was conducted. Results on continuous measurements were presented as mean ± standard deviation and results on categorical measurements were presented as number (frequency). Parametric data were analyzed using unpaired "*t*" test. $p < 0.05$ was considered as significant. The sample size required in this study ($n = 3$ in each group) was based on the assumption of recurrence in all congenital anterior glottic webs, a reduction in recurrence by 50% with botulinum toxin, a type I (alpha) error of 0.05, a type II (beta) error of 0.2, and a study power of 0.8.

Results

Three females and three males were included in the study (Table 1). The age at presentation and surgery ranged from 2 to 19 years, with a mean of 11.17 ± 6.04 years. The preoperative mean percentage of anterior glottic web in both groups was 46.67 ± 2.36, i.e., grade II. The postoperative mean percentage of anterior glottic web was 26.67 ± 6.24 in Group I and 13.33 ± 4.71% in Group II (Fig. 1).

The mean percentage of the length of the glottis involved by web improved in both groups postoperatively, with a significantly greater improvement seen in Group II (difference in improvement between both groups postoperatively = 13.34%, $t = 2.955$, $p = 0.0417$) (Table 2). The only patient to have undergone intraoperative tracheostomy (case no. 4), was successfully decannulated 3 days following keel removal. All patients had subjective improvement of voice. No complications were encountered (Figs 2 and 3).

Discussion

Embryologically, failure of epithelial lamina recanalization has been implicated in the pathogenesis of laryngeal webs and stenosis. Milczuk et al., while studying five patients with a web with subglottic extension, observed that this abnormality could be explained by anomalous persistence of subglottic extension of the epithelial lamina after embryogenesis.[9] Sanudo et al. described a vestibulotracheal duct (i.e., a ventral extension of the infraglottis), which in the event of failed development allows influx of precartilaginous cells into the area, forming the anterior subglottis, thereby explaining the formation of a congenital anterior glottic web with subglottic stenosis.[4,10]

A laryngeal web may present clinically with biphasic stridor, dysphonia, recurrent pneumonia or respiratory insufficiency, or a combination of symptoms, and the severity depending upon the extent of the laryngeal web.[1] The commonest symptom in patients with an anterior glottic web is dysphonia,[11] which was the only symptom in patients in our study. Miyamoto et al. in their study involving pediatric patients with an anterior glottic web identified a microdeletion on chromosome 22q11.2 in 65% of their cases, which is associated with velocardiofacial syndrome and DiGeorge syndrome.[12] However, these features were conspicuously absent in our cases.

In our study, the mean age at presentation was 11.17 years. Certain studies have similarly shown delayed presentation which can be attributed to the lack of parental awareness and an apprehension about appropriate endoscopic examination. However, other studies on congenital anterior glottic webs have shown presentation from birth to 3 years of age. This reaffirms that a thorough evaluation including endoscopic laryngeal examination for an etiological diagnosis is mandated in all infants with dysphonia, weak cry, or stridor.[4]

Anterior glottic webs are classified according to the system proposed by Cohen, which is based on the percentage of vocal cord involvement and the presence of subglottic extension, i.e., type I is an anterior web involving ≤35 of the glottis, type II involves 35 to 50 of the glottis, type III covers 50 to 75 of the glottis, and type IV covers 75 to 90 of the glottis.[13] The thickness of the web and the associated subglottic extension are the key determinants of appropriate management. Webs of types II, III, and IV often extend

Table 1: Case details

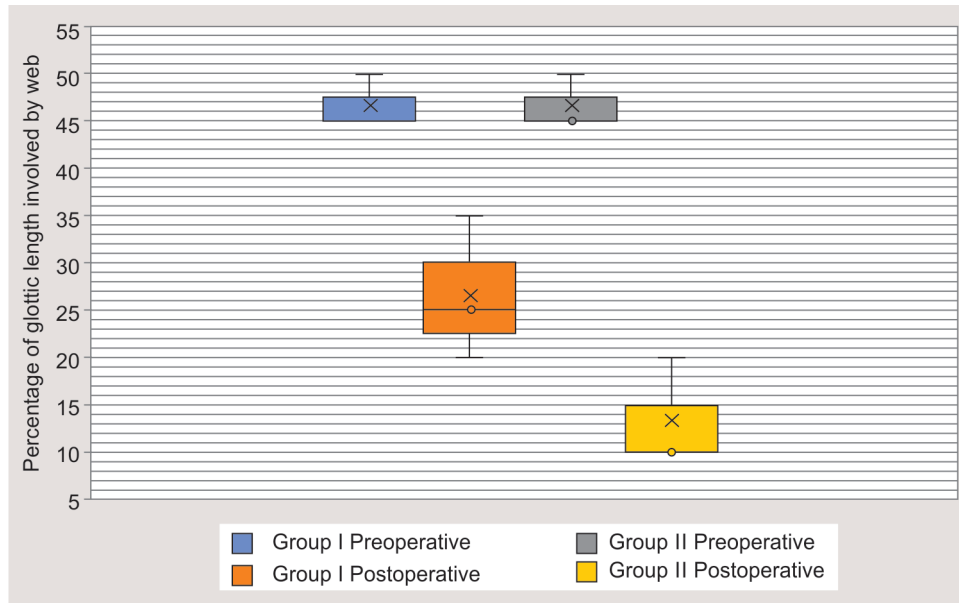| | | | | Percentage of glottic length involved by web | |
Case no.	Group	Age at surgery	Gender	Preoperatively	Postoperatively
1	I	5 years	Male	45	25
2	II	19 years	Male	50	20
3	I	12 years	Female	45	20
4	I	2 years	Female	50	35
5	II	17 years	Male	45	10
6	II	12 years	Female	45	10

Fig. 1: Pre- and postoperative web in both groups

Table 2: Comparison of pre- and postoperative percentage of glottic length involved by web

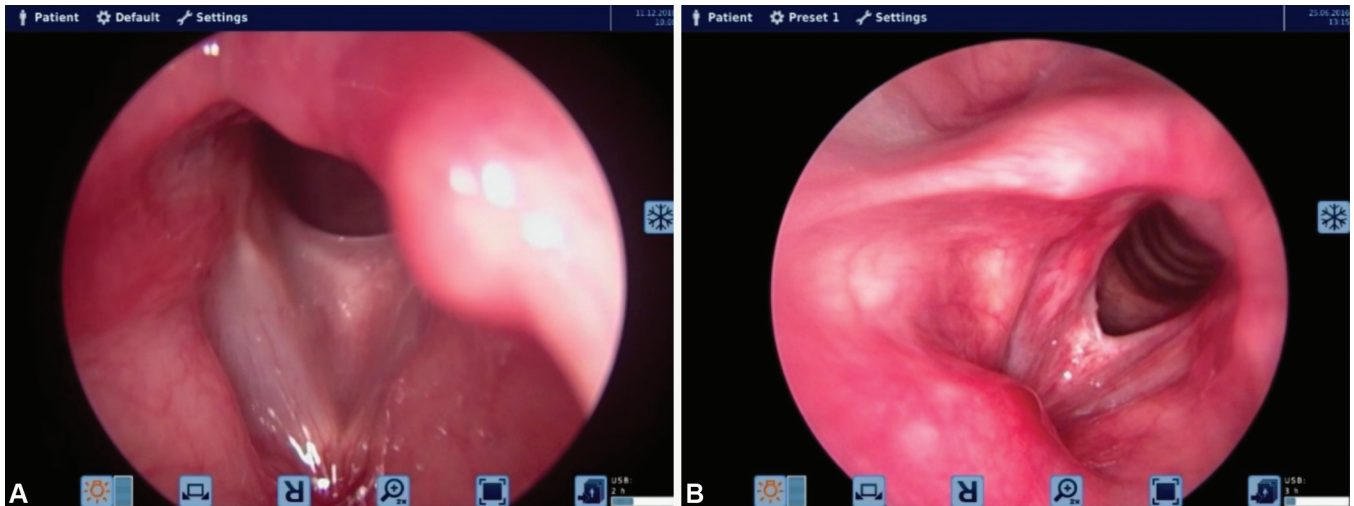| Group	Percentage of glottic length involved by web (mean ± standard deviation)		Difference (%)	t test	p value	Significance
	Preoperatively	Postoperatively				
I	46.67 ± 2.36	26.67 ± 6.24	20.00	5.192	0.0065	Significant
II	46.67 ± 2.36	13.33 ± 4.71	33.34	10.961	0.0004	Significant

into the subglottis in increasing degrees, causing a decrease in its luminal area. Cohen's classification lacks reliability as the visible glottic extension of the web is invariably not a forewarning of the subglottic extension.[4] Virtual bronchoscopy and three-dimensional reformatting of computerized tomography images may aid in its recognition but are fraught with limitations especially the inability to allow dynamic evaluation of associated tracheomalacia and degradation of image quality due to transmitted cardiac pulsations, particularly in infants and toddlers.[14] Therefore, the final decision on appropriate management can be taken only during on-table microlaryngeal surgery after incision and palpation of the web for accurate assessment of subglottic extension,[4] as was performed in our cases.

Even with diverse options evolving over the years for the treatment of anterior glottic webs, the quintessential approach still remains controversial. The currently available endoscopic techniques and external approaches each have their own advantages (primarily its safety) and disadvantages, with none free of the innate possibility of some degree of readhesion of the iatrogenically created raw, de-epithelialized surfaces on both sides of the dissected vocal folds.[1] Endoscopic techniques include an endolaryngeal mucosal flap, endoscopic placement of a keel, and Mouney and Lyons endoscopic modification of Dedo's technique.[4] Webs of Cohen's grade II and above are endoscopically divided with keel placement, while Cohen's grade IV webs warrant an open surgery.[1] However, the therapeutic outcome of endoscopic management primarily depends on thickness of the web rather than the Cohen's grading. External techniques entail laryngofissure and
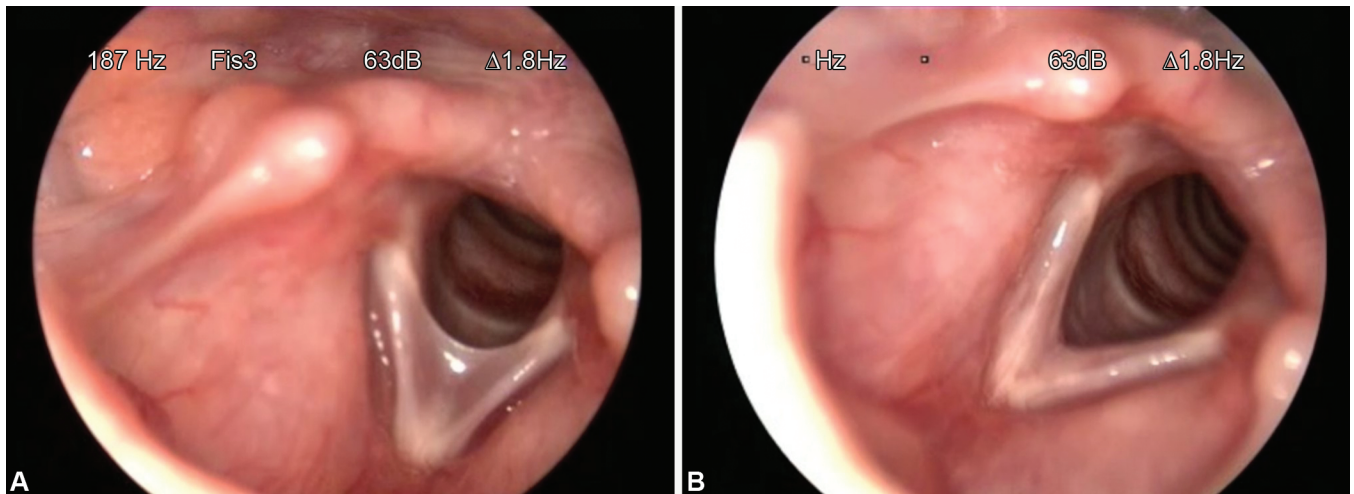
web division with keel insertion or stenting and laryngotracheal reconstruction.[4]

Simple division of the web with application of mitomycin-C, an antiproliferative agent which reduces scar formation and fibrosis, has predominantly yielded poor results.[15] However, studies by Hardillo et al.[16] and Spector et al.[17] have proved the effectiveness of mitomycin-C in the prevention of recurrence. Of the four techniques tested, Alkan et al. concluded that the best long-term outcome has been obtained with keel placement.[1] The primary advantage of endoscopic anterior glottic web lysis and keel placement is the elimination of an external surgical procedure. Edwards et al. concluded that though the laryngofissure approach is of proven safety and efficacy, similar outcomes can be obtained with the endoscopic technique while circumventing the morbidity associated with an open procedure.[11] Several problems may arise with keel placement, i.e., it can be displaced, its external fixation requires larynx perforation with possible infections and it can irritate the surrounding mucosa with subsequent formation of granulation.[5] None of these complications were observed in our cases. Numerous studies recommend that the keel remain *in situ* for 3 to 4 weeks. However, research has shown that the epithelialization process is completed by the end of 12 to 14 days following which the probability of web recurrence is negligible, thereby allowing relatively safe keel removal at 2 weeks,[11] as was practiced in our cases.

Overall, the conundrum existing with regard to satisfactory treatment of anterior glottic webs is fundamentally due to recurrent scar formation aggravated by mobility of the vocal folds. Botulinum

Figs 2A and B: Laryngoscopy images from a case in Group I. (A) Preoperative; (B) Postoperative

Figs 3A and B: Laryngoscopy images from a case in Group II. (A) Preoperative; (B) Postoperative

toxin type A is a known potent neurotoxin that acts on the presynaptic cholinergic nerve terminal, decreasing the release of acetylcholine and thereby causing a neuromuscular blocking effect. It has been safely used in humans to treat conditions like spasmodic dysphonia, etc.[18] Its injection into the thyroarytenoid muscle results in a chemodenervation-induced temporary flaccid paralysis of this adductor muscle and hence prevents overadduction. This property of botulinum toxin has been successfully harnessed in the prevention of posterior synechiae (without sacrificing any laryngeal components) and thus minimizing recurrence while treating posterior glottic stenosis.[8,19] Similarly, a standard dose of 2.5 MU of botulinum toxin A injected into each thyroarytenoid muscle intraoperatively in our study group to prevent adduction and consequent anterior glottic web recurrence has yielded a successful result.

Although no objective measurement of voice was performed in this study, all six cases reported subjective voice improvement postoperatively, as observed in studies by Chen et al.[20] and Su et al.[21]

Conclusion

Botulinum toxin, because of its paralytic effect on the thyroarytenoid muscle when injected, decreases the possibility of web reformation.

It can therefore be used as an added armamentarium in the treatment of anterior glottic webs, along with the established techniques including keel placement.

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