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Botulinum Toxin Injections to Cricothyroid Muscles for Relief of Bilateral Recurrent Laryngeal Nerve Paralysis

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Bilateral Reküren Laringeal Sinir Paralizisinde Düzelme İçin Krikotiroid Kaslara Botulinum Toksin Enjeksiyonu

Amaç: İnsanlarda bilateral abdüktör paralizisine bağlı hava yolu obstrüksiyonunu rahatlatmak üzere botulinum toksini kullanımının araştırılması.

Çalışma Tasarımı: Prospektif ön klinik çalışma. Çalışmada bilateral reküren laringeal sinir paralizisi olan ve her iki krikotiroid kasta normal nöronal aktivite sergileyen EMG'si bulunan bir hasta yer almıştır.

Gereç ve Yöntem: Perkütan yaklaşım kullanılarak elektromiyografik rehberlikle her iki krikotiroid kasa botulinum toksini enjeksiyonu yapıldı. Anterior komissür merkez olarak kullanılarak vokal kordların açısı bilgisayar programı ile doğrulanan goniometre kullanılarak enjeksiyon öncesinde ve sonrasında üç pozisyonda ölçüldü: dinlenme, maksimum abdüksiyon ve addüksiyon.

Sonuç: Botulinum toksini bilateral reküren laringeal sinir paralizisinin olumsuz etkilerini iyileştirebilir.

Anahtar Sözcükler: Botulinum toksini, laringeal EMG, bilateral abdüktor paralizisi.

Abstract

Objectives: Investigation of botulinum toxin use to relieve obstruction of the airway from bilateral abductor paralysis in humans.

Study Design: Prospective preliminary clinical study. The study included a patient in which EMG demonstrated bilateral recurrent laryngeal nerve paralysis and normal neuronal activity of both cricothyroid muscles.

Materials and Methods: Injection of botulinum toxin to both cricothyroid muscles were performed under electromyograpic guidance by using a percutaneous approach. The angles of the cords using the anterior commissure as the center were measured in three positions; resting, maximum abduction, and adduction before and after injection using a goniometer confirmed with computer program.

Conclusion: Botulinum toxin could relieve the devastating effects of bilateral recurrent laryngeal nerve paralysis.

Key Words: Botulinum toxin, laryngeal EMG, bilateral abductor paralysis.

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Introduction

Since Cohen reported the lateralization of the true vocal cords with botulinum toxin in animal model,[1,2] we failed to find in the literature any further experiments on its use to relieve obstruction of

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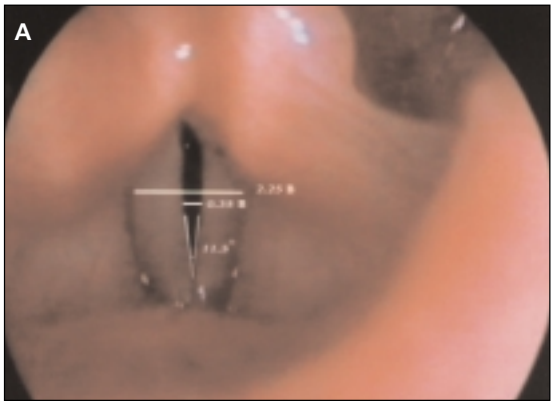
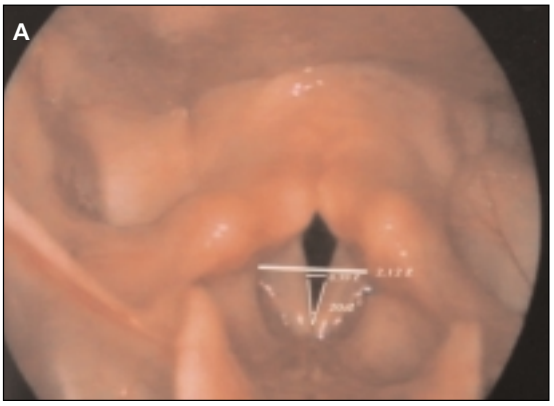
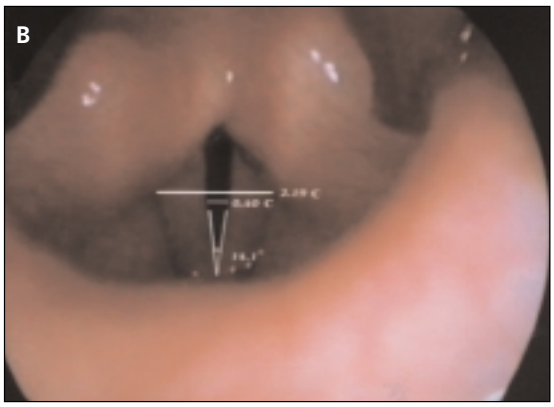
the airway from bilateral recurrent nerve paralysis of the larynx. This experiment was undertaken in order to determine whether the toxin can improve the airway in subjects with bilateral abductor paralysis in human larynx. Clostridium botulinum produces a very powerful neurotoxin.[3] There are numerous antigenically identifiable strains. These are named A,B,C1,C2,D,E,F and G. All are proteases with a similar structure, composed of a light chain linked by a disulfide bond to a heavy chain.[4] Botulinum toxin A has powerful paralytic effects on the human. The type A botulinum toxin has been crystallized in stable form and is available for clinical use.[3-5] Injected into muscle, BTX-A causes flaccid paralysis by inhibiting release of acetylcholine from nerve terminals. This process involves four steps: binding, internalization, membrane translocation, and protease activity.[6] Binding occurs specifically and irreversibly to peripheral cholinergic nerve terminals, a process mediated by the toxin heavy chain. The toxin molecule then undergoes receptor mediated endocytosis. Once this has occurred, the toxin light chain translocates to the cytoplasmic side of the endosome, a process in which the heavy chain again plays a role. There, the light chain acts as a zinc-dependent protease to cleave one of three proteins that form the synaptic fusion complex involved in the exocytosis of acetylcholine, preventing neurotransmitter release and rendering the nerve terminal nonfunctional. Each serotype has its own specific site of action. The target of BTX-A is the synaptosome-associated protein of 25 kD molecular mass, commonly abbreviated SNAP-25. Recovery takes place in two distinct phases. Initially, accessory terminals sprout from the axon with the damaged presynaptic terminal and act to stimulate muscle. After approximately 28 days, the main terminal begins to slowly recover its ability to release neurotransmitter, probably through synthesis of new, intact SNAP-25, and the sprouts gradually disappear. After a little more than 90 days, a length of time that correlates well with that of the clinically observed duration of effect, recovery is essentially complete. Although the concentration may vary according to the physicians' needs, in the treatment of the small muscles of the larynx, it was found that 2.5 u/0.1 mL is useful.[7-9] Dose requirements of the toxin are higher in mongrel dog as an animal model because probably has antibodies to this toxin.[1] Long term exposure to the toxin will cause reversible denervation atrophy of the muscle.[10] Prolonged effects can be achieved by multiple injections of the toxin. Stimulation of the cricothyroid muscle approximates the cricoid ring to the lower border of the thyroid. Unilateral stimulation of the cricothyroid muscle affects elevation and deviation of the ring toward the stimulated side. Bilateral stimulation cause elongation of the vocal cord and approximation of the vocal processes to each other.[3] Paralysis of the cricothyroid muscle, served by the external branch of the superior laryngeal nerve decreases the tension of true vocal cord and allows the cord to take a more lateral position. Cutting the external division of the superior laryngeal nerve or removing the cricothyroid muscle also produces gradual lateral bowing of the ipsilateral vocal cord and thereby opens the airway In this study the toxin was injected into the cricothyroid muscle to block neuromuscular transmission at the motor end plate and paralysis of the cricothyroid muscle was achieved.[1] This project was undertaken to study the effects of botulinum toxin in order to relieve the obstructive phenomenon resulting from bilateral abductor paralysis and thus eliminate the need for an artificial airway. The toxin was injected into the cricothyroid muscle to block neuromuscular transmission at the motor end plate and paralysis of the cricothyroid muscle was achieved. We believe that this is the first report of the use of this toxin in the treatment of bilateral abductor paralysis in clinical trial. We report the preliminary results.

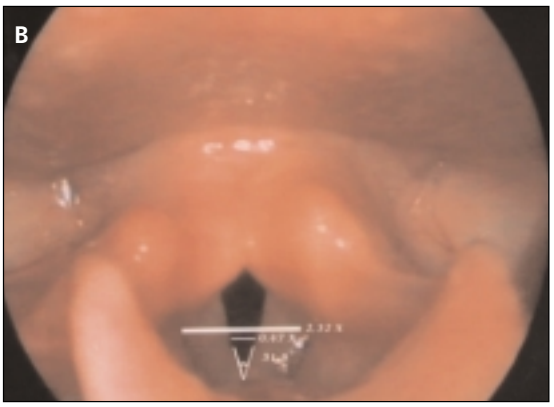
Materials and Methods

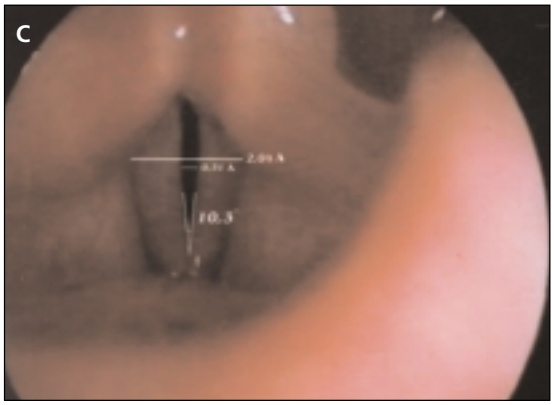
A 22-year old female, who had undergone bilateral subtotal thyroidectomy 2 years ago, had progressive dyspnea for two months prior to her initial admission. She had stridor but her voice was satis-











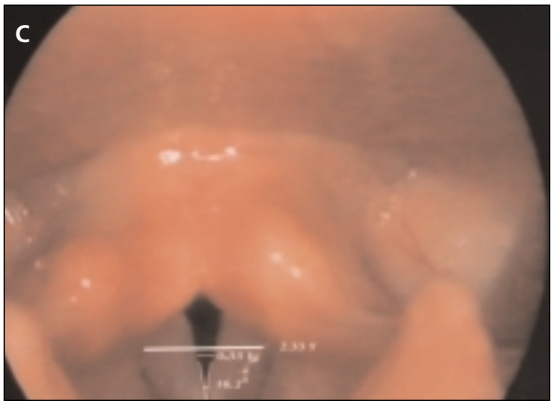


Figure 1. The larynx of the patient was videotaped at the beginning of the study at the three defined cord position; resting (**A**), maximum abduction (**B**), and maximum adduction (**C**). The angles of the cords using the anterior commisure as the center were measured in three positions using a goniometer confirmed with computer program.

Figure 2. The larynx of the patient was videotaped at the three defined cord positions; resting (**A**), maximum abduction (**B**), and maximum adduction (**C**) 120 hours after botulinum toxin injection. The angles of the cords using the anterior commisure as the center were measured in three positions using a goniometer confirmed with computer program.

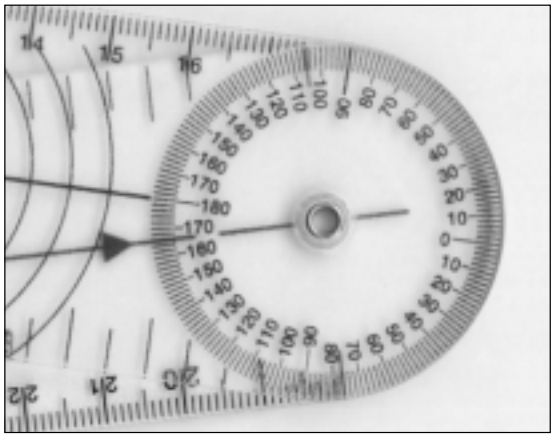


Figure 3. Goniometer to measure angle.

factory. Examination of her larynx with laryngoscope showed a 2-3 mm glottis with fixed cords bilaterally. The clinical diagnosis was based on history, general and neurological examination, laryngoscopy and voice evaluation. No evidence of other neurological disease was found. The patient underwent an emergency tracheotomy with immediate relief of airway distress. After 5 days the patient had stabilized and the larynx of the patient was videotaped at the beginning of the study at the three defined cord positions; resting, maximum abduction, and maximum adduction (Figure 1). Spirometric analysis of the respiratory potential of the patient was performed to evaluate glottal airflow between the cords in both inspiration and expiration. Barium esophagography was done. Chest X-ray examination was performed immediately after barium esophagograph for detection of possible aspiration and dysphagia. There was no evidence of leakage to trachea. Voice quality was evaluated subjectively. Then she was evaluated by laryngeal EMG that is an objective test for differentiation of whether an immobile cord is due to the neurogenic dysfunction or cricoarytenoid fixation.[11] Laryngeal EMG demonstrated bilateral recurrent larengeal nerve paralysis and normal neuronal activity of both cricothyroid muscles. Then botox injection needle (Oxford Instruments, Surrey, GU229JU, England), a needle converted into an electromyography probe was used to enter the muscle under EMG control and deposit toxin. Injection of botulinum toxin to both cricothyroid muscles was performed under electromyographic guidance by using a percutaneous approach. Needle position was verified with high-pitched phonation. Proper placement was confirmed by increasing motor unit potential recruitments during performance of a scale while vocalizing "E". Improper placement resulted in activation with neck flexion, suggesting that the electrode has entered the strap musculature of the neck.[12,13] BOTOX (Allergan Botox Ltd, Westport, Ireland), Botulinum Toxin Type A purified neurotoxin complex was reconstituted with 2 ml 0.9% sodium chloride saline to a final concentration of 50U/ml. Initially, an attempt was made to weaken or paralyze cricothyroid muscles with an injection of 5 U in 0.1 ml. into each cricothyroid muscle. The larynx

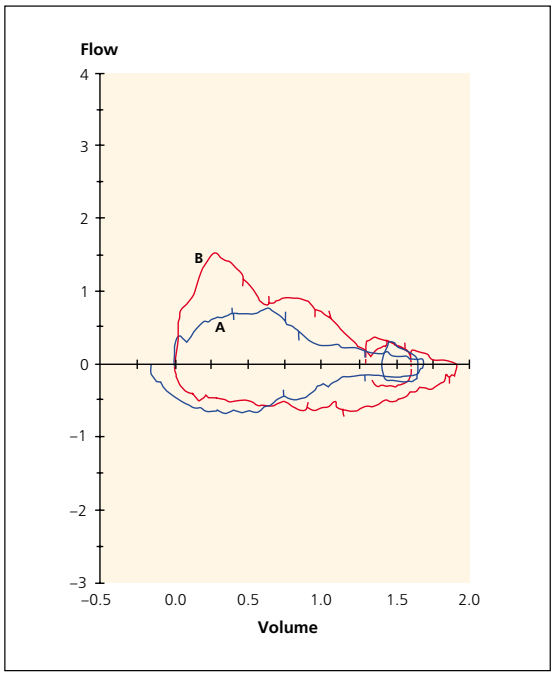


Figure 4. Spirometric analysis is performed. Flow-volume curve before (**A**) and 120 hours after (**B**) botulinum toxin injection.

of the patient was videotaped at the three defined cord positions; resting, maximum abduction, and maximum adduction (Figure 2) and spirometric analysis of the patient was done 120 hours after botulinum toxin injection as, one to three days usually pass before any clinical effect is seen. The angles of the cords using the anterior commissure as the center were measured in three positions; resting, maximum abduction, and adduction before and after injection (Table 1) using a goniometer (Figure 3) confirmed with computer program. Spirometric analysis was performed again after the tracheostomy tube was removed and tracheostomy is occluded by fingertip in order not to let air passage.

Table 1. The angles of the cords using the anterior commissure as the center were measured in three positions before and after 120 hours of botulinum toxin injection using a goniometer and confirmed with computer program.

	Before injection	After injection	Change
Resting	11.5	20.2	**76%**
Maximum abduction	14.1	31.5	**123%**
Maximum adduction	10.3	16.2	**57%**

Results

The procedure was tolerated well. There was no evidence of dysphagia and aspiration. Postoperative infection or toxic reaction to the drug injection was not seen. Voice quality of the patient did not change significantly. In spirometric analysis, flow-volume curve (Figure 4) which is an accurate, noninvasive technique for diagnosis and subsequent assessment of therapy in patients with fixed upper airway obstruction improved moderately.[14] Symptoms and direct visualization of the obstruction before and after botox injection correlated with the changes seen in flow-volume curve. Attention has been given to forced inspired volume in one second (FIV1).[15] FIV1 improved notably (298%) which is one of the most important values in following the response to treatment in upper airway obstruction (Table 2). The position of the cords was further apart at the three defined cord positions;

Table 2. Spirometric analysis is performed before and 120 hours after botulinum toxin injection.

		Ref	Pre	%Ref	Post	%Ref	%Change
FVC	Liters	2.97	1.71	57	1.91	64	12
FEV1	Liters	2.58	0.75	29	1.06	41	41
FEV1/FVC	%	84	44		55		
FEV1/SVC	%		29				
FEF25-75%	L/sec	3.91	0.36	9	0.43	11	19
IsoFEF25-75	L/sec		0.36		0.76		111
FEF25%	L/sec	5.71	0.69	12	1.20	21	74
FEF50%	L/sec	4.14	0.42	10	0.78	19	86
FEF75%	L/sec	2.03	0.18	9	0.27	13	46
FEF200-1200	L/sec		0.43		0.85		100
PEF	L/sec	6.23	0.77	12	1.54	25	100
FET25-75%	Sec		2.39	63	2.25		-6
FIVC	Liters	2.97	1.86		1.92	65	3
FIV1/FIVC	%		9		26		288
FIV1	**Liters**		**16.75**		**49.92**		**298**
PIF	L/sec		0.69		0.65		-6
FEF/FIF50			0.83		1.24		49
FVLECode			111000		111000		

resting, maximum abduction, and maximum adduction which produces much larger airway with the greatest change can be seen in maximum abduction.

Discussion

Injury to both recurrent laryngeal nerves can have devastating effects on the basis laryngeal functions of respiration. Bilateral vocal cord paralysis frequently leads to airway obstruction. Botulinum toxin could relieve the devastating effects of laryngeal bilateral abductor paralysis. Paralysis of neighboring muscles is the major complication of its use. Spread of toxin from the injected muscle has been suggested as an etiology. This is prevented by delivering small doses and careful injection of the toxin under EMG guidance.[16] The effect of the drug is temporary, especially its use in some patients with spontaneous reversible bilateral vocal cord paralysis would be ideal. It may be applicable to the infant with temporary paralysis of the larynx caused by birth trauma and thus may eliminate the need for an artificial airway. Cutting the external division of the superior laryngeal nerve or removing the cricothyroid muscle also produces gradual lateral bowing of the ipsilateral vocal cord and thereby opens the airway but botulinum toxin injection to cricotyroid muscles does not change anatomy of the larynx and is not permanent. This technique is relatively safe, easy to perform and effective. It has almost immediate response and no systemic toxicity when locally injected.

Conclusion

In our preliminary experiment, the use of botulinum toxin was proven to be relatively safe, effective in maintaining localized paralysis of the muscle into which it was injected, and temporary and effective in lateralizing the true vocal cord. A large number of patients and long-term studies are needed.

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