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Dysphagia

Prolonged Effect of Botulinum Toxin Injection in the Treatment of Cricopharyngeal Dysphagia: Case Report and Literature Review

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Abstract. Cricopharyngeus (CP) muscle spasm can lead to severe dysphagia. Myotomy of the CP muscle was the treatment of choice. Recently, botulinum toxin type A (BtxA) has been used for CP spasm. It usually brings improvement in deglutition but most patients require reinjection in 3–5 months. We report a 35-year-old man who had an arteriovenous malformation hemorrhage in the brain stem resulting in CP spasm and consequently severe dysphagia. He received BtxA injection and deglutition and nutrition remained good one year after treatment. A literature review analyzing 28 patients and our patient showed negative correlations between age and BtxA dose and between age and duration. Efficacy was positively correlated with duration and BtxA dose was positively correlated with pretreatment severity. In conclusion, physicians would use higher doses on patients with more severe cases but use lower doses on older patients. Those who obtained better post-treatment results would enjoy longer effective duration. Thus, the effective duration of the BtxA is multifactorial.

Key words: Botulinum toxin type A — Cricopharyngeus muscle spasm — Dysphagia — Deglutition — Deglutition disorders.

Botulinum toxin type A (BtxA) is of significant therapeutic value in the management of a variety of hyperkinetic disorders such as blepharospasm, torticollis, writer's cramp, orofacial dystonia, and spasmodic dysphonia [1]. It is also efficacious in the treatment of facial nerve disorders such as synkinesis or hemifacial spasm. It has also been applied in the treatment of esophageal motility disorders such as achalasia, hypertensive lower esophageal sphincter, and upper esophageal sphincter spasm [2,3,4]. Dysphagia due to hyperactivity of the upper esophageal sphincter (UES), more specifically the cricopharyngeal (CP) muscle, can be seen in a variety of neurological disorders such as cerebral vascular accidents, amyotrophic lateral sclerosis, multiple sclerosis, acoustic neuroma, and Parkinson's disease. It can also occur after surgical procedures for the head and neck such as in resections for oropharyngeal and supraglottic carcinoma as a result of iatrogenic injury to the pharyngeal or recurrent laryngeal nerves. Some causes of dysphagia are idiopathic [4–7]. Traditionally, surgical myotomy of the CP muscle is the treatment of choice for hyperactivity of the UES due to various causes [8,9]. However, CP myotomy is invasive and is not always effective [8]. BtxA was introduced in 1989 by Schneider et al. [4] for patients with spasticity, hypertonus, or delayed relaxation of the UES. The intervention usually brings improvement in deglutition but most patients require reinjection in 3–5 months [5]. We report a patient with a brain stem stroke who was left with CP sphincter spasm and consequently severe dysphagia. He received BtxA injection and deglutition and nutrition remained good one year after injection. This is unusually long for BtxA treatment in terms of its mode of action in which neuromuscular transmission is usually restored within 3–4 months. Thus, we did a literature review to explore factors affecting the efficacy and duration of BtxA treatment.

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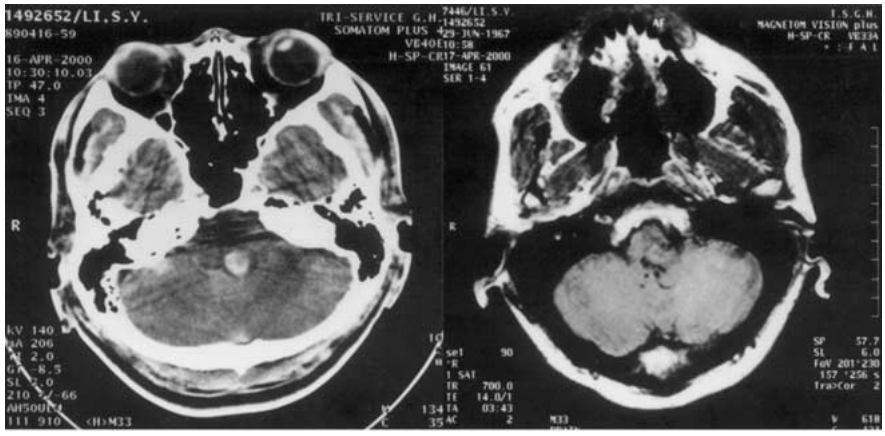

Fig. 1. A Preoperation cranial computed tomography shows a hematoma in the left posterior pons. **B** The postoperation magnetic resonance imaging of the head reveals an arteriovenous malformation in the left pontomedulla.

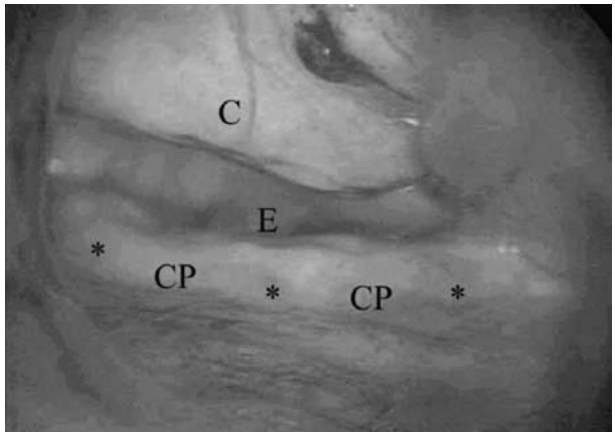

Fig. 2. Under laryngoscopic view, the cricoid (C), esophageal lumen (E), and bulk of the cricopharyngeal muscle (CP) are clearly visible. The asterisks indicate the three injection sites.

Case Report

The patient was a 35-year-old man who suffered from severe dysphagia with a disability rating scale (DRS) score of 4 [4] for about one and a half years after an episode of acute consciousness impairment from an arteriovenous malformation (AVM) hemorrhage in the left posterior pontomedulla (Fig. 1A,B). He received emergency surgery for decompression and removal of blood clots. After the surgery, he gradually regained consciousness and motor functions. However, he was left with severe swallowing disturbance and required nasogastric tube feeding. Afterward, he had a significant body weight loss from a premorbid baseline of 73–74 kg to 66 kg (body height = 175 cm). The neurological examination on admission revealed leftward gaze palsy, left abducens palsy, and left peripheral-type facial palsy. Mild dysarthria with minimal hypernasality was noted. Mild vocal cord palsy on the left side was also observed during laryngoscope examination. Hemihypoesthesia to pinprick and thermal stimulation over the right side of his body was also detected. No definite motor deficits, including weakness, muscle tone change, or abnormal tendon reflex, were detected. He could not drink even 20–30 ml of water without having to spit it out. Videofluoroscopic swallowing study (VFSS) showed almost no passage of barium into the esophagus. It showed severe dysphagia with lower pharyngeal constrictor dysfunction or upper esophageal spasm. With written informed consent from the patient we performed an intrasphincteric BtxA injection.

About two weeks after the injection, the patient started oral feedings. He could drink small swallows of water and eat semisolid food such as pudding (DRS: 2). His swallowing continued to improve and he could eat solid food the third week (DRS: 1). His body weight returned to 74 kg two months after the treatment (DRS: 0–1) and remained around 72 kg. At the one-year followup, his neurological condition was stable. He could eat and swallow almost normally except for hard solid food at a rapid speed (DRS: 0–1). He had no complications such as acid regurgitation or belching from aerophagia. He received another VFSS about 10 months after the injection of BtxA (described below).

BtxA Injection Method

BtxA was obtained from Dysport (IPSEN, Berkshire, UK) as freeze-dried lyophilized preparation. For clinical use, BtxA activity is defined in units, 1 unit representing the estimated median lethal dose for mice. Shortly before use, the toxin was dissolved with 2.5 ml of 0.9% sterile saline solution (without preservative), equivalent to 500 units. Under general anesthesia and direct laryngoscopic guidance, the bulk of the CP muscle was clearly identified. Botulinum toxin 0.6 ml, containing an equivalent dose of about 120 units of Dysport per site, was injected into the left and right lateral sides and the dorsomedial part of the muscle (Fig. 2).

VFSS

VFSS was performed with thin barium (5 ml), thick barium (5 ml), and paste barium (5 ml) in the lateral view and thin barium (5 ml) in the anterior–posterior view. The preinjection VFSS (about 3 months prior to the injection) showed almost no passage of barium into the esophagus with occasional pharyngeal–oral reflux, and laryngeal penetration (Fig. 2A). There was no aspiration. Poor contractility of the lower pharyngeal segment with massive movement was also noted. VFSS showed a severe dysphagia with lower pharyngeal constrictor dysfunction or upper esophageal spasm.

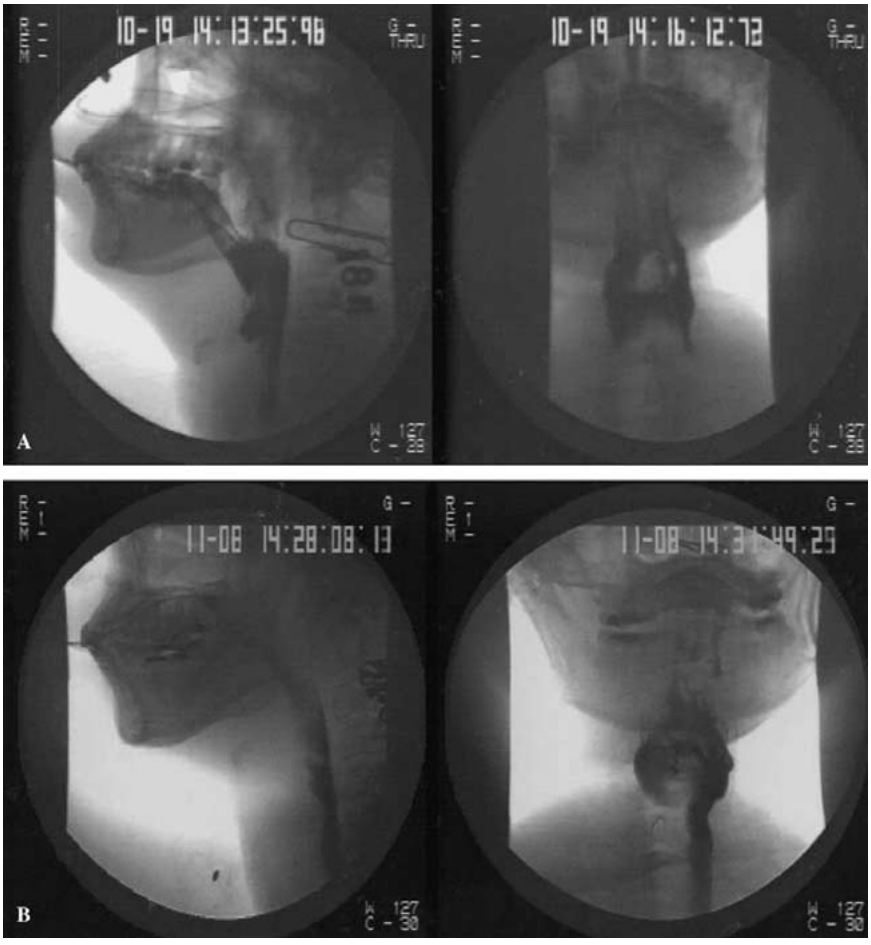

Fig. 3. A Videofluoroscopic swallowing study (VFSS) about 3 months prior to injection shows almost no passage of barium into the esophagus, pharyngeal–oral reflux, and mild laryngeal penetration. There is no aspiration. Poor contractility of the lower pharyngeal segment with massive movement is noted. **B** VFSS, about 10 months after the injection shows left predominant passage into esophagus with a mild oropharyngeal dysphagia and minimal laryngeal penetration.

The first postinjection VFSS (about one month after the injection) revealed left-side predominant bilateral passage into the esophagus but no pharyngeal–oral reflux or pharyngeal–nasal reflux. The second postinjection VFSS (about 10 months after the injection) showed left predominant passage into the esophagus with mild oropharyngeal dysphagia (Fig. 2B).

We reviewed the literature, focusing on the efficacy of the BtxA injection and duration of effects. For this purpose, we searched MEDLINE using keywords cricopharyngeus, cricopharyngeal muscle, spasm, spasticity, hypertonus, dysphagia, deglutition disorder, swallowing disorder and BtxA; we found 7 reported series or cases reports [4,5,10–14]. We analyzed 28 of 30 cases from 5 reports [4,10–12,14] in which there was detailed information on clinical diagnosis, severity, injection dose, efficacy, and duration of response to BtxA intervention. Together with our patient, 29 cases were subjected to further analysis (Table 1). The clinical severity of dysphagia was transformed into Schneider's 5-point scale (0–4) DRS [4] for comparison. In Schneider's DRS, score 0 indicates normal function, patient without complaints; score 1: no functional impairment, but subjective dysphagia when swallowing solid and/or liquid foods; score 2: mild functional impairment for solid and/or liquid food; score 3: marked disability with moderate aspiration; and score 4: severe functional impairment with complete inability to swallow, considerable aspiration, and pneumonia. The efficacy was computed by subtracting the post-treatment DRS score from the pre-treatment score. Doses were transformed into Dysport equivalent units with the ratio of Dysport:Botox = 3:1 [15, 16]. In cases with multiple treatments, the dose with the longest effective duration was used for analysis.

Results

Descriptive statistics were reviewed in 6 women and 23 men with an average age of 62.8 ± 14.6 years. The mean pretreatment DRS score was 3.48 ± 0.63 and mean post-treatment DRS score 1.48 ± 1.30 with a mean Dysport equivalent dose of 110.2 ± 79.1 units. The mean effective duration was 4.2 ± 2.9 months with a mean efficacy of 2.00 ± 1.34 change in DRS score. For exploring efficacy in patients with different clinical diagnoses, patients were further categorized into three groups; Group 1, patients with cerebrovascular diseases, i.e., strokes (n = 10); Group 2, patients with malignancies in the tongue base, oropharynx, hypopharynx, supraglottis, or larynx who suffered peripheral nerve injuries after surgery in the upper neck (n = 13); Group 3 consisted of patients

Table 1. Data from 31 patients with CP dysphagia

Case	Age (yr)	Sex	Diagnosis	Severity Pre[a]	Dose	Severity Post[a]	Duration (months)
S1	29	M	Stroke, VI, X, XII	4	80/160	3	4.5
S2	52	M	Supraglottic ca, partial laryngectomy	3	80	0	5
S3	47	F	Oropharynx ca, lower jaw resection	3	80	0	5
S4	71	M	Acoustic neuroma, IX, X	4	80	4	0
S5	55	M	Stroke, tetraplegia	3	80	2	5
S6	45	M	Brachyesophagus	2	80	2	0
S7	62	M	Oropharynx ca, lower jaw resection	2	100	0	5
Ah1	48	M	Stroke	4	240	0	3
Ah2	41	M	HIV	4	180/300	0	4
Ah3	67	M	Carotid EA, pharyngeal dysmotility	3	180/180	0	3
Ah4	65	M	Stroke	4	180/180	4	2
Ah5	68	F	Tongue base ca + R/T, S/T	4	120/180	4	14
At1	78	M	Bulbar palsy + apraxic gait	3	30	1	2.5
At2	85	M	Progressive dysphagia + myotomy	3	30	2	2.5
At3	75	M	Stroke; cerebellum, brainstem	4	45/60	2	1.5
At4	70	M	Peripheral neuropathy	3	60	3	0.5
At5	?	?	Medullar tumor, IX, X, XI, XII	4	?	?	?
P1	52	M	Hypopharynx ca + C/T, R/T	4	30–75	3–1	3–6
P2	72	M	Stroke	3	45	1	3
P3	58	M	Idiopathic	4	45	2	4
P4	76	M	Idiopathic	3	45	2	3
P5	63	M	Larynx ca + total laryngectomy	4	45	1	6
P6	69	M	Larynx ca + total laryngectomy	4	45/90	2/1	4
P7	71	F	Amyotrophic lateral sclerosis	4	75	3	4
P8	75	M	Stroke, vocal palsy, unilateral	4	45/90	2/1	4
P9	58	M	Larynx ca + total laryngectomy	4	60	1	6
P10	86	F	Parkinson's, Stroke	3	45	2	3
P11	80	F	Idiopathic cervical dysphagia	4	45	0	4
P12	69	F	Idiopathic cervical dysphagia	4	60	*	*
R	68	F	Oculopharyngeal muscular dystrophy	3	60	1	4
C	35	M	Stroke, VI, VII, IX, X	4	360	0	12

?: not specified; *: lost followup; Dose: Dysport equivalent units (Dysport : Botox = 3:1).
[a]Severity following S: Schneider [4]; Ah: Ahsan [11]; At: Atkinson [10]; P: Parameswaran [12]; R: Restivo [14]; C: Chiu; ca: carcinoma; C/T: chemotherapy; R/T: radiotherapy; S/T: surgery; EA: endarterectomy.

with other causes such as idiopathic dysphagia ($n = 6$). A Kruskal–Wallis test showed no significant differences in the three groups for age, pretreatment DRS score, post-treatment DRS score, efficacy, dose of BtxA applied, and effective duration. However, Spearman rho correlation showed that age was negatively correlated with the dose of BtxA ($r = -0.598$, $p < 0.0001$) and with duration of efficacy ($r = -0.463$, $p = 0.006$). Efficacy was positively correlated with duration of efficacy ($r = 0.448$, $p = 0.007$). Dose was not significantly correlated with efficacy or duration but it was positively correlated with the pretreatment DRS score ($r = 0.370$, $p = 0.024$). In other words, although physicians used higher doses in more severe cases, they also tended to use lower doses on older patients, probably because the elderly had decreased muscle mass. The elderly seemed to have shorter effective duration. Those who obtained better post-treatment results enjoyed longer duration of effectiveness.

Discussion

UES spasm can have serious consequences leading to complete inability to swallow, as in our case. BtxA has been demonstrated to be therapeutic for CP muscle spasm and hypertonicity. It can be used in evaluating patients for permanent treatment such as CP myotomy [5].

BtxA binds to the motor nerve terminal with its heavy chain [17], which is selective for cholinergic nerve terminals. It is then internalized via endocytosis [18], forming a vesicle inside the nerve terminal and releasing its light chain into the cytoplasm [19]. It blocks acetylcholine release by cleaving SNAP-25, a cytoplasmic protein on the cell membrane, for release of this transmitter [20]. Paralysis occurs as the complete loss of miniature endplate potential starts. Therefore, the therapeutic effects of muscle weakness are usually evident after a certain latency ranging from a few days to 2–3 weeks. Chemical denervation

of the neuromuscular junction by BtxA results in an expansion of the end-plate region and growth stimulation of collateral axonal sprouts [21]. A nerve sprout eventually establishes a new neuromuscular junction, and muscle activity gradually returns. But evidence also suggests the new nerve sprout retracts and the original junction returns to functionality [22]. Theoretically, effects are not permanent, lasting an average of 3–4 months, which is the time needed for re-establishing new neuromuscular junctions and muscle activity. Our patient maintained good deglutition for more than one year after BtxA injection. He was the second youngest patient in our analysis and responded very well to the BtxA injection of 360 Dysport units. Although our patient received the highest dose of BtxA among all reviewed cases, the relation between the dose and duration of efficacy was not substantiated by statistics. Some cases in our reviewed series used doses of BtxA up to 240 (Case Ah1) or 300 (Case Ah2) units but they sustained a duration of about 3–4 months (Table 1). Thus, the unusually prolonged duration of effectiveness cannot be fully elucidated just through the denervation and sprouting of the motor endplate. Other possible mechanisms should be considered.

In our patient, the lesion involved the dorsal pontomedulla affecting the corticoreticular tract and fibers leading to the dorsal recticulospinal tract, which is of crucial importance in the facilitation of the inhibitory function from cortical neurons. The influence of cortical motor areas over tone is principally mediated by a powerful mechanism in the bulbar reticular formation. Loss of inhibitory influence from the corticoreticular tract leaves the facilitating effects of the ventromedial reticular formation unopposed [23]. In this situation, severe spasticity with hypertonia is greatest in the antigravity or postural-maintaining muscles (composed of mainly slow fibers) such as the closure maintaining CP muscle. Reduction of muscle tone following treatment with BtxA results from effects of muscle denervation as well as inhibition of the fusiform system and muscle spindle [24]. Motor innervation of the intrafusal muscle fibers comes from small-diameter motor neurons, called gamma motor neurons to distinguish them from the large-diameter alpha motor neurons. The gamma motor neurons provide a mechanism for adjusting the sensitivity of the muscle spindles. When a muscle is stretched, e.g., the CP muscle is stretched during passage of a bolus coming down from the oropharynx, the Ia afferents in the muscle increase their firing rates leading to excitation of the alpha motor neurons and contraction of the muscle via the reflex arc. The activation of gamma motor neurons causes increased intensity or lowered threshold of the sensory afferents' firing from the intrafusal spindles. This coactivation of alpha and gamma motor neurons serves as a feedback mechanism from muscle spindles to reinforce the activation of the alpha motor neurons. The swallowing peristaltic waves come down from the oropharynx and the upper pharynx to the CP muscle. The CP orifice completes the bolus passage through three steps. First is relaxation and opening of the orifice. At this point, an abnormal hyperactive stretch reflex of the muscle would impede the relaxation and thus prevent opening of the orifice. Second, after the opening, the CP muscle contracts and closes the orifice. Finally, it returns to the resting state [25]. In the human CP muscle, the horizontal inner layer contains more slow fibers while the outer oblique layer contains more fast fibers [26]. Interestingly, sprouting is generally slower in fast-twitch muscles, which are more crucial in the stretch reflex, than in slow-twitch muscles with predominantly type I fibers [27]. Thus, muscle-fiber-type specificity unique in human CP muscle could be an additional factor in prolonged effectiveness.

In conclusion, the effective duration of BtxA injection in relieving CP spasm is multifactorial, especially in cases with brain stem stroke. It differs from a simple denervation–reinnervation process as in cases of hemifacial spasm. It also differs from hyperkinetic disorders such as spasmodic dysphonia in that hypertonia results from rigidity but not spasticity. It also differs from spastic paresis, which occurs in areas other than the CP muscle where fiber-type specificity is not seen. A prolonged effect has also been seen in upper [11] and lower esophagus spasm [28]. Further study on the mechanism is still necessary to clarify this interesting and important phenomenon.

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