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Sarah Youssof

Sarah Youssof, M.D.
Candidate

Biomedical Sciences
Department

This thesis is approved, and it is acceptable in quality and form for publication:

Approved by the Thesis Committee:

Leslie Morrison, M.D., Chairperson

David Bear, Ph.D.

Mark Schuyler, M.D.

SAFETY OF BOTULINUM TOXIN FOR DYSPHAGIA IN OCULOPHARYNGEAL MUSCULAR DYSTROPHY

by

SARAH YOUSSOF

B.A.
M.D.

THESIS

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DEDICATION

For my mother and father

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Lee, for his encouragement and sage advice.

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Sarah Youssof

B.A., Chemistry and Physics, Harvard University, 1997

M.D., Medicine, University of California-San Francisco, 2004

M.S., Biomedical Sciences, University of New Mexico, 2013

Abstract

Despite multiple studies reporting marked benefit of botulinum toxin (BTX) for treatment of cricopharyngeal dysphagia, little is known about its safety for this indication. We examined the safety of cricopharyngeal BTX for dysphagia in oculopharyngeal muscular dystrophy (OPMD). We reviewed records of patients with OPMD who received cricopharyngeal BTX. Twenty-four patients underwent 66 procedures. Overall adverse event frequency was 44%. The most common adverse events were dysphonia (24%) and worsened dysphagia (14%). Logistic regression demonstrated that dose was a significant predictor of worsened dysphagia (P=0.036) and of the composite event of dysphonia or worsened dysphagia (P=0.009). There was a non-significant trend for dose as a predictor of dysphonia (P=0.073). 59% of procedures were associated with symptomatic improvement. While BTX appears to be beneficial for treatment of dysphagia in OPMD, caution is warranted when injecting the cricopharyngeus muscle due to dose-related risk of dysphonia or worsened dysphagia.

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Chapter 1

Introduction

Oculopharyngeal muscular dystrophy (OPMD) is a late-onset, autosomal dominant muscle disease characterized by dysphagia, ptosis, and limb weakness.[1,2] Radiologic and manometric studies of OPMD have shown that the upper esophageal sphincter (UES) obstructs bolus transit.[3,4] The cricopharyngeus (CP) muscle, the major component of the UES, is normally tonically active at rest and relaxes during swallow.[5] In OPMD, weak pharyngeal contractions are ineffective in transporting boluses across the UES.[6,7] Surgical myotomy of the UES lowers sphincter pressure and improves swallowing in OPMD[6-11] but poses serious risks, including post-surgical fistula, pneumonia, and death.[12]

An alternative to surgery is chemical myotomy using botulinum toxin (BTX). To date, 33 observational studies have reported 300 adults, including 6 with myopathy,[13-17] who received BTX for cricopharyngeal dysphagia of disparate causes. The aggregate improvement rate was 73% (Table 1, Appendix). All 6 patients with myopathy improved, including 2 with OPMD.[13,14]

Given the proximity of the CP muscle to posterior arytenoid and inferior pharyngeal muscles and the risk of local diffusion of BTX, transient dysphonia and worsened dysphagia are expected adverse events (AEs).[18] Remarkably, only 11% of individuals in prior studies experienced any AE, and only 3% experienced dysphonia or

worsened dysphagia (Table 1, Appendix). No prior study of cricopharyngeal BTX examined the relationship between dose and AEs.

We encounter many patients with OPMD at our center due to high disease prevalence in New Mexico.[19] We sought to better characterize risks associated with cricopharyngeal BTX in OPMD.

Chapter 2

Material and Methods

We reviewed health records of all patients with a confirmed diagnosis of OPMD[20] who had at least 1 cricopharyngeal BTX injection at our center between January 1, 2000 and December 31, 2011. This study was approved by the local institutional review board. Requirement for informed consent was waived since the study was a retrospective chart review. AEs and symptomatic improvement were ascertained by reviewing notes in the 6-month period after each procedure. Two of the 66 procedures (3%) were not followed by a clinic visit. In these cases, missing data were imputed as follows: no AE and no improvement.

We used generalized linear mixed models (GLIMMIX in SAS 9.3) to identify predictors of worsened dysphagia, dysphonia, and a composite event defined as dysphonia or worsened dysphagia. These models account for correlations due to repeated procedures on the same individual. If the likelihood ratio test of the random effect (individual patient) in the generalized linear mixed model was not significant, then the model was reduced to simple logistic regression, where each procedure was considered to be independent. All initial models included the following variables: age, gender, dose, procedure type (percutaneous or endoscopic), injection site (bilateral or unilateral), and time since last injection. We included the last term to account for residual effects from any previous injection. We used backward elimination to remove non-significant predictors. *P*-values < 0.05 were considered significant.

Chapter 3

Results

Sixty-six BTX injections were administered to 24 patients with OPMD (mean age 63 ± 8 years, mean age of dysphagia onset 52 ± 5 years, 14 men, 100% Hispanic). Of 19 patients who had videofluoroscopic swallowing studies before the first injection, 14 had CP prominence or reduced CP opening.

The median number of procedures per patient was 3 (range 1-13). For individuals with more than 1 procedure, the median time between treatments was 6 months (range 2-39). Median onabotulinumtoxinA (Botox®, Allergan, Irvine, CA) dose was 20 units (range 10-30). All but 3 procedures were performed by the same otolaryngologist. Toxin was injected either percutaneously with electromyographic guidance (88%) or endoscopically with direct visualization (12%). Sixty-eight percent of procedures involved bilateral cricopharyngeal injections; the rest were unilateral.

AEs occurred after 44% of procedures, and 19 of 24 individuals had at least 1 AE. The most common AEs were transient dysphonia and worsened dysphagia, which occurred after 24% and 14% of procedures, respectively. Other AEs included dizziness or syncope (8%), reflux (5%), injection site pain (5%), rash (2%), and laryngospasm (2%). In 10 cases, the duration of dysphonia after treatment was recorded and ranged from 1 week to 4 months. There were 2 serious AEs requiring brief hospital visits (one patient with 3 episodes of syncope immediately after the procedure and a second patient with laryngospasm and respiratory distress within 1 day of the procedure).

Likelihood ratio tests of the random effect (individual patient) in the generalized linear mixed models were not significant for any of the 3 dependent variables (worsened dysphagia: P=0.15, dysphonia: P=0.34, composite event of dysphonia or worsened dysphagia: P=0.23). Logistic regression demonstrated that dose is a significant predictor of worsened dysphagia (P=0.036) and of the composite event (P=0.009). There was a non-significant trend for dose as a predictor of dysphonia alone (P=0.073). See Figure 1 below. Age, gender, procedure type, injection site, and time since last injection were not significant predictors in any model. For a 10-unit increase in dose, the odds ratio (OR) for worsened dysphagia was 3.92 (95 % C.I. 1.09,14.05), the OR for dysphonia was 2.40 (95% C.I. 0.92, 6.26), and the OR for the composite event was 3.49 (95% C.I. 1.36, 8.95).

Physicians documented symptom improvement following 59% of procedures.

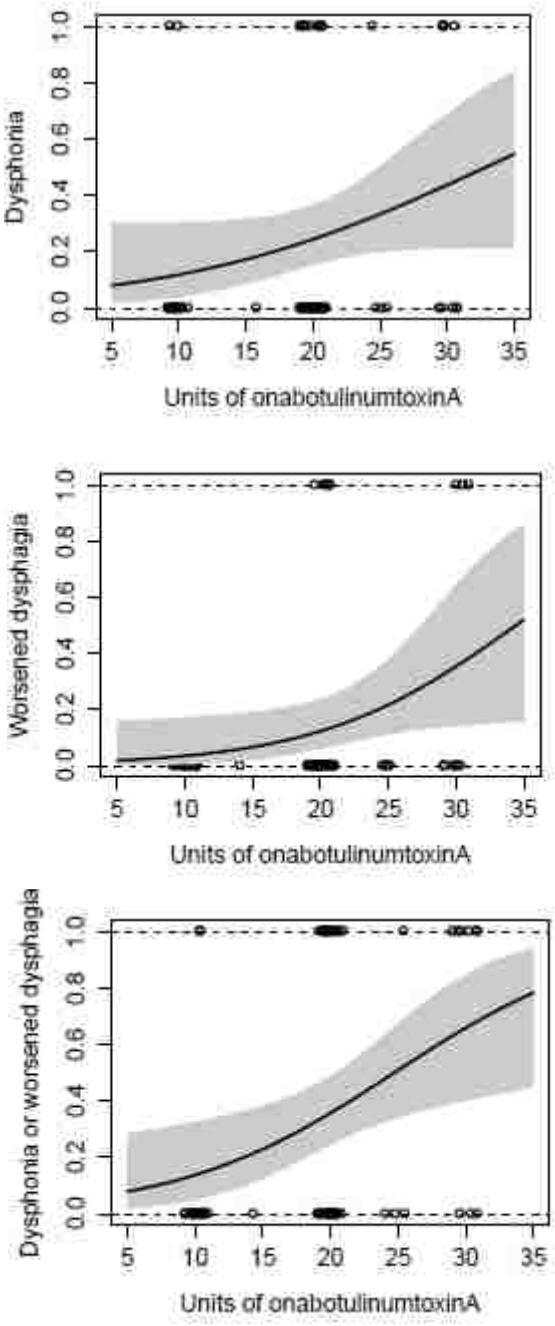

Figure 1. Logistic dose-response models were fit to the data. Estimated probabilities of dysphonia (top panel), worsened dysphagia (middle panel), and the composite event of dysphonia or worsened dysphagia (lower panel) increase as a function of dose. The y-axes represent estimated probabilities. Solid black curves represent the results of the models for each adverse event. Gray regions represent 95% confidence intervals. Open circles indicate actual doses for each procedure and are displayed with jitter to make identical values visible.

Chapter 4

Discussion

This study examined the safety of BTX for treatment of cricopharyngeal dysphagia in a large number of cases with a single myopathy. Our observed 44% AE rate contrasts with the 11% AE rate reported in prior studies (Table 1, Appendix).

Doses in prior studies varied from 5 to 120 Botox®-equivalent units. While some have predicted that injection of 100 units in the CP muscle would likely cause dysphonia and worsened dysphagia through local toxin diffusion,[18] none of 54 individuals who received ≥100 units in prior studies were reported to experience an AE (Table 1, Appendix). Furthermore, only 3% of 300 individuals in prior studies were reported to experience dysphonia or worsened dysphagia, and no study demonstrated a link between dose and AEs (Table 1, Appendix). In contrast, our study shows that dysphonia and worsened dysphagia are dose-related AEs, and provides estimates for the magnitude of AE risk at different doses.

AE risk may depend on the etiology of dysphagia. Given the peripheral mechanism of action of BTX, individuals with muscle or lower motor neuron disorders may be more prone to AEs. Yet, none of 6 individuals with myopathy who received cricopharyngeal BTX in prior studies experienced dysphonia or worsened dysphagia.[13-17] Moreover, a recent study that evaluated the benefit of cricopharyngeal BTX in 20 patients with amyotrophic lateral sclerosis reported no complications in the sub-group with lower

motor neuron bulbar weakness.[21] Ours quantifies the risks of cricopharyngeal BTX specifically in muscle disease.

Although our study could not assess efficacy since there was no untreated comparison group and validated dysphagia outcome measures were not used, subjective improvement followed 59% of procedures. Given potential for benefit, a controlled trial is warranted. Until then, we emphasize the need for caution when administering BTX to the CP muscle.

Appendix

Table 1. Summary of 33 prior studies of botulinum toxin injection for treatment of cricopharyngeal dysphagia in adults.[a]

Study	N	CNS[b]	PNS[c]	Non-neurologic[d]	Dose[e]	Method[f]	Improved[g]	AE[h]	AE Type[i]
Dunne et al., Lancet 1993; 342(8870):559	1	1	0	0	16	P	1	0	
Schneider et al., Ann Otol Rhinol Laryngol 1994;103(1):31-35	7	2	1	4	27-40	E	5	1	heartburn
Crary et al., Arch Otolaryngol Head Neck Surg 1996;122(7):760-763	5	0	0	5	25-30	P	4	2	worsened dysphagia (1), regurgitation (1)
Atkinson et al., J Otolaryngology 1997;26(4):273-276	5	3	1	1	5-20	P	4	1	left vocal cord paresis
Blitzer et al., Otolaryngol Head Neck Surg 1997;116(3):328-330	6	2	0	4	10	P	6	0	
Brant et al., Dis Esophagus 1999;12(1):68-73	1	1	0	0	100	E	1	0	
Alberty et al., Laynrgoscope 2000;110(7):1151-1156	10	1	1	8	30	E	10	1	dysphagia
Restivo et al., Gastroenterology 2000;119(5):1416	1	0	1	0	10	P	1	0	
Ahsan et al., Otolaryngol Head Neck Surg 2000;122(5):691-695	5	2	1	2	40-100	E	5	0	
Shaw et al., Dysphagia 2001;16(3):161-167	12	2	3	7	25-50	E or O	10	3	pharyngeal tear (2); worsened dysphagia (1)
Haapaniemi et al., Dysphagia 2001;16(3):171-175	4	2	2	0	14-50	E	3	1	temporary urinary retention
Moerman et al., Eur Arch Otorhinolaryngol 2002;259(1):1-3.	4	0	0	4	100	E	4	0	
Restivo et al., N Engl J Med 2002;346(15):1174-1175	4	4	0	0	10	P	4	0	
Parameswaran et al., Ann Otol Rhinol Laryngol 2002;111(10):871-874	12	4	0	8	10-30	E	11	1	neck cellulitis after concomitant surgery
Marchese-Ragona et al., Ann Otol Rhinol Laryngol 2003;112(3):258-263	5	0	0	5	10-16	P	5	2	aerophagia (1), regurgitation (1)
Zaninotto et al., J Gastrointest Surg 2004;8(8):997-1006	21	8	5	8	5-10	P	9	1	death from aspiration (attributed to underlying disease)

Table 1. Summary of 33 prior studies of botulinum toxin injection for treatment of cricopharyngeal dysphagia in adults.[a]

Liu et al., Can J Gastroenterol 2004;18(6):397-9	2	0	2	0	100	E	2	0	
Chiu et al., Dysphagia 2004;19(1):52-7	1	1	0	0	120	E	1	0	
Murry et al., Am J Otolaryngol 2005;26(3):157-62	13	7	3	3	100	P	11	0	
Kim et al., Arch Phys Med Rehabil. 2006;87(10):1346-51	8	8	0	0	100	E	5	0	
Masiero et al., J Rehabil Med 2006;38(3):201-3	2	2	0	0	25-30	P	2	0	
Restivo et al., Diabetes Care 2006;29(12):2650-2653	12	0	12	0	20	P	12	0	
Restivo et al., J Neurol 2006;253(3):388-389	2	2	0	0	10	P	2	0	
Suzukia et al., Brain Dev 2007;29(10):662-665	1	0	1	0	5	P	1	1	transient worsened dysphagia
Krause et al., Dysphagia 2008;23(4):406-410	1	1	0	0	60	E	1	0	
Oh et al., Am J Phys Med Rehabil 2008;87(11):883-889	2	0	2	0	NR[j]	NR	0	0	
Terre et al., Scand J Gastroenterol 2008;43(11):1296-1303	10	10	0	0	100	E	8	0	
Alfonsi et al., J Neurol Neurosurg Psychiatry. 2010;81(1):54-60	34	34	0	0	15	P	17	0	
Natt et al., Auris Nasus Larynx 2010;37(4):500-503	15	0	0	15	100	P	13	1	pain at injection site
Restivo et al., Eur J Neurol 2011;18(3):486-490	14	14	0	0	20	P	14	0	
Kelly et al., Ann Otol Rhinol Laryngol 2013;122(2):100-108	49	NR	NR	NR	15-100	P or E	32	16	transient worsened dysphagia (number NR), chest pain (2), congestion (1), belching (number NR), increased mucus (number NR), reflux (number NR)
Woisard-Bassols et al., Eur Arch Otorhinolaryngol 2013;270(3):805-815	11	4	7	0	25-60	P	5	3	transient worsened dysphagia (2), reflux (2)
Restivo et al., Neurology 2013;80(7):616-620	20	13	7	0	10	P	11	0	

[a] We searched PubMed (1947-July 2013) using the search strategy: "Botulinum Toxins"[Mesh] AND "Deglutition Disorders"[Mesh]. The search yielded 386 titles. Inclusion criteria: any observational (including case reports or case series) or experimental study of botulinum toxin for cricopharyngeal dysphagia. Exclusion criteria: studies in infants or children. References of relevant articles were reviewed. 33 articles met inclusion/exclusion criteria and underwent full-text review.
[b] CNS: central nervous system etiology (e.g. stroke, bulbar palsy, Parkinson's disease)
[c] PNS: peripheral nervous system etiology (e.g. cranial nerve palsies, spinal muscular atrophy, myopathy,)
[d] Non-neurologic etiology (e.g. Zenker's diverticulum, post-pharyngectomy, post-laryngectomy; idiopathic cricopharyngeal dysfunction)
[e] Dose: Botox®-equivalent units (Dysport®:Botox® conversion ratio 3:1)
[f] Method: P – percutaneous (guidance by electromyography, computed tomography, or videofluoroscopy); E – endoscopic; O – open surgical technique
[g] Improved: number of individual reported to have clinically improved (note: outcome measures varied across studies)
[h] AE: number of individuals reported to have experienced at least one adverse event
[i] AE Type: type of adverse event (number of adverse events in parentheses)
[j] NR: not reported

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