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SAFETY OF BOTULINUM TOXIN FOR DYSPHAGIA IN OCULOPHARYNGEAL MUSCULAR DYSTROPHY

SARAH YOUSSEF, MD¹, RONALD M. SCHRADER, PhD², CAROL ROMERO-CLARK, MS, CCC-SLP³, GULMOHOR ROY, MD¹, and MICHAEL SPAFFORD, MD⁴

¹Department of Neurology, MSC 10 5620, 1 University of New Mexico, Albuquerque, New Mexico 87131

²Clinical and Translational Science Center, University of New Mexico Health Sciences Center, Albuquerque, New Mexico

³Department of Speech-Language Pathology, University of New Mexico Health Sciences Center, Albuquerque, New Mexico

⁴Department of Surgery, University of New Mexico Health Sciences Center, Albuquerque, New Mexico

Abstract

Introduction—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).

Methods—We reviewed records of patients with OPMD who received cricopharyngeal BTX.

Results—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 nonsignificant trend for dose as a predictor of dysphonia ($P=0.073$). 59% of procedures were associated with symptomatic improvement.

Conclusions—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.

Keywords

botulinum toxin; dysphagia; neuromuscular diseases; oculopharyngeal muscular dystrophy; therapeutics

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 OPMD⁶⁻¹¹ but poses serious risks, including postsurgical 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% (see Supp. Table S1, which is available online). 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 (Supp. Table S1). 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.

MATERIALS AND METHODS

We reviewed health records of all patients with a confirmed diagnosis of OPMD²⁰ 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 because 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 nonsignificant predictors. *P*-values <0.05 were considered significant.

RESULTS

Sixty-six BTX injections were administered to 24 patients with OPMD (mean age, 63±68 years, mean age of dysphagia onset 52±65 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 months). Median onabotulinumtoxinA (Botox®, Allergan, Irvine, California) dose was 20 units (range, 10–30 units). 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 (1 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 nonsignificant trend for dose as a predictor of dysphonia alone (*P* = 0.073, see Figure 1). 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% CI, 1.09–14.05), the OR for dysphonia was 2.40 (95% CI, 0.92–6.26), and the OR for the composite event was 3.49 (95% CI, 1.36–8.95).

Physicians documented symptom improvement following 59% of procedures.

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 (Supp. Table S1).

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,¹⁸ 100 units in prior studies were reported to experience an AE (Supp. Table S1). 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 (Supp. Table S1). 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 Our study quantifies the risks of cricopharyngeal BTX specifically in muscle disease.

Although this study did 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

AE	adverse event
BTX	botulinum toxin
CI	confidence interval
CP	cricopharyngeus
OR	odds ratio
OPMD	oculopharyngeal muscular dystrophy
UES	upper esophageal sphincter

FIGURE 1.

Logistic dose-response models were fit to the data. Estimated probabilities of dysphonia, worsened dysphagia, and the composite event of dysphonia or worsened dysphagia increase as a function of dose. The y-axis represents 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.