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# The Long-term Efficacy of Botulinum Toxin Injection to Treat Retrograde Cricopharyngeus Dysfunction

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## Abstract

*Objectives.* To report the percentage of patients with symptom relief 6 or more months after botulinum toxin injection into the cricopharyngeus muscle for retrograde cricopharyngeus dysfunction (R-CPD).

*Study Design.* Retrospective case series of consecutively treated patients.

*Setting.* Tertiary care laryngology clinic.

*Subjects and Methods.* A review was performed of the first 200 patients who were diagnosed with R-CPD and treated with botulinum toxin injection into the cricopharyngeus muscle by a single surgeon. The study group was limited to those for whom a minimum of 6 months has elapsed since the injection. Items assessed were efficacy, safety, complications, and duration of benefit.

*Results.* Of 200 patients treated, (99.5%) gained the ability to burp and 95% experienced relief of the cardinal symptoms of R-CPD: inability to belch, socially awkward gurgling noises, abdominal/chest pressure and bloating, and excessive flatulence. For those who experienced relief, 159 (79.9%) maintained a satisfactory ability to burp after 6 months. Of those who did not maintain the ability, 12 underwent a second injection, 1 patient underwent 3 subsequent injections, and 3 patients underwent partial myotomy. No patients experienced complications of botulinum toxin injection itself, and 4 patients had complications from esophagoscopy or anesthesia.

*Conclusion.* In a case series of 200 patients with retrograde cricopharyngeus dysfunction, 99% experienced relief of the cardinal symptoms and 79.9% experienced lasting relief of their symptoms beyond pharmacologic duration of action after a single injection of botulinum toxin into the cricopharyngeus muscle. Relief can be reestablished in the remainder via additional injection or cricopharyngeus myotomy.

## Keywords

belch, cricopharyngeus muscle dysfunction, burp

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In March 2019, Bastian and Smithson[1] first described the syndrome now known as retrograde cricopharyngeus dysfunction (R-CPD), along with the details about the first 51 patients who were diagnosed and subsequently treated with botulinum toxin injection. In that study, and to the present, patients are diagnosed syndromically, that is, by a constellation of symptoms of inability to belch, socially awkward gurgling noises, abdominal/chest pressure and bloating, and excessive flatulence. Once diagnosed in this way, botulinum toxin injection into the cricopharyngeus muscle is both confirmatory (diagnostic) and therapeutic. As a result of the daily misery caused by the disorder as well as the dissemination of information about it by its sufferers on social media, patients have continued to present from around the nation and globe to seek treatment for this disorder. To date, 274 patients have been treated at the Bastian Voice Institute for R-CPD, with 25 more having been evaluated but not yet treated.

These patients have all presented with virtually identical debilitating symptoms, and none had received a prior diagnosis or successful treatment despite extensive workup, suggesting that this syndrome remains unknown to the medical community. Our objective is to report on long-term results for the first 200 of a larger caseload of patients, all of whom have been followed for at least 6 months after botulinum toxin injection.

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## Materials and Methods

This is a retrospective case series of consecutively treated patients with R-CPD. Institutional review board approval was obtained from AspireIRB. Consecutive patients were identified via a prospective database maintained for clinical purposes on patients with this diagnosis. An extensive questionnaire was filled out by all patients at their initial appointment, including symptomatology, age at which symptoms started, presence of symptoms in infancy (if known), previous tests performed and/or diagnoses received, perceived severity of condition and motivation to pursue treatment, and family history of this condition. At the visit, the patient questionnaire was reviewed, and a diagnosis was achieved based on the constellation of symptoms. Swallowing was evaluated using a videoendoscopic swallow study including brief upper esophagoscopy to identify any gross abnormalities and to ensure that all mechanisms of swallowing are intact. Patients who chose to proceed with treatment then underwent an outpatient endoscopic injection of 50U in the first 165 patients and 75U of botulinum toxin in the most recent 35 patients using the technique previously described by Bastian and Smithson.[1] Esophageal dilation was not performed in any patient. Patients were counseled on the expected postoperative effect of the injection, including the nature and timing of burp onset, alterations in swallowing (described by patients as the sense that food ''hangs'') that typically resolve over the course of 1 to 2 weeks, worsening of existing reflux, and a sense of heaviness or a ''lump'' in the throat. Patients were counseled to chew carefully and wash solids down with liquids to manage the swallowing changes, which typically resolve in the early weeks. They were then followed up at 1 week, 6 weeks, 3 months, 6 months, and then yearly and asked to report on the presence or absence of the symptoms of R-CPD and any other concerns or complications.

Data were collected from this initial questionnaire and the patients' charts on gender, age at diagnosis, previous studies performed, rating of severity/motivation for treatment (on a scale of 1 to 7), status of symptoms at follow-up intervals, response to treatment, and reported complications or issues. Repeat procedures, if any, were also recorded. Simple statistics were performed using Excel.

## Results

A total of 200 consecutive patients with retrograde cricopharyngeus dysfunction underwent treatment between November 2015 through September 2019. Patient characteristics are included in **Table 1**. These patients came from 40 states and 5 foreign countries. Ages ranged from 9 to 64 years, with an average age of 31 years. There were 6 patients younger than 18 years, although only 1 patient was younger than 15 years. Patient follow-up after initial injection ranged from 6 to 52 months, with an average follow up of 14.4 months and a median follow up of 12.0 months.

Before presenting to our clinic, most patients had sought medical attention, with 81.1% (163 patients) having had at least 1 diagnostic procedure or therapy (**Figure 1**). A total of 59.7% (120 patients) had undergone a procedure prior to presentation, and 53.5% (108 patients) had tried empiric trials of medications. Of note, 15.8% had already undergone 4 or more procedures. Specifically, of all patients, 60.8% had undergone gastrointestinal endoscopy, 11.8% manometry, 37.3% a swallow study, and 2% some type of radiographic imaging. Per patient report, most of these tests were ''normal,'' or if treatment was provided, it did not resolve their symptoms. Notably, all patients thus far have been self-referred after encountering the syndromic features mostly from fellow sufferers on the internet.

**Table 1.** Patient Profile for Cohort of 200 Patients With Retrograde Cricopharyngeus Dysfunction.

| Total patients | 200 |
|---|---|
| Male | 105 (52.5%) |
| Female | 95 (47.5%) |
| Age, y | |
| Range | 9-64 |
| Average | 31 |
| Median | 29 |
| Follow-up, mo | |
| Average | 14.4 |
| Median | 12.0 |

When asked about the severity of their symptoms on a scale of 1 to 7, with 7 being very severe, patients rated their symptoms an average of 6.0 with a median score of 6 (range, 3-7). When asked about their motivation to solve this issue on the same scale, the average patient rating was 6.7, with a median score of 7 (range, 3-7; **Figure 2**).

Most (98.0%) patients described lifelong or early childhood onset of symptoms, and 2.0% were uncertain of the onset or thought it was within the past 5 years. Those patients treated at younger than 18 years all noted a lifelong presence of symptoms. Interestingly, 41.8% of patients had learned from parents that they were difficult or impossible to burp as an infant. Their parents had described some combination of gassiness, colic, incessant crying from pain, projectile vomiting, and difficulty burping. Of the patients, 25.4% did not have information about their infancy, and 32.8% had been told they burped normally as infants.

Of these 200 patients, 199 (99%) gained an ability to burp, 93% (185 patients) of those within 1 week from surgery. The other 7.0% (14 patients) gained this ability within the first 4 weeks. Most (189 patients, 95.0%) experienced significant relief of the cardinal symptoms of R-CPD after their initial injection of botulinum toxin: they were able to belch and their socially awkward gurgling noises, abdominal/chest pressure and bloating, and excessive flatulence vanished or diminished dramatically. Many described the overall benefit as ''life changing.'' Of the rest of the patients, 7 patients (3.5%) were able to burp yet had only

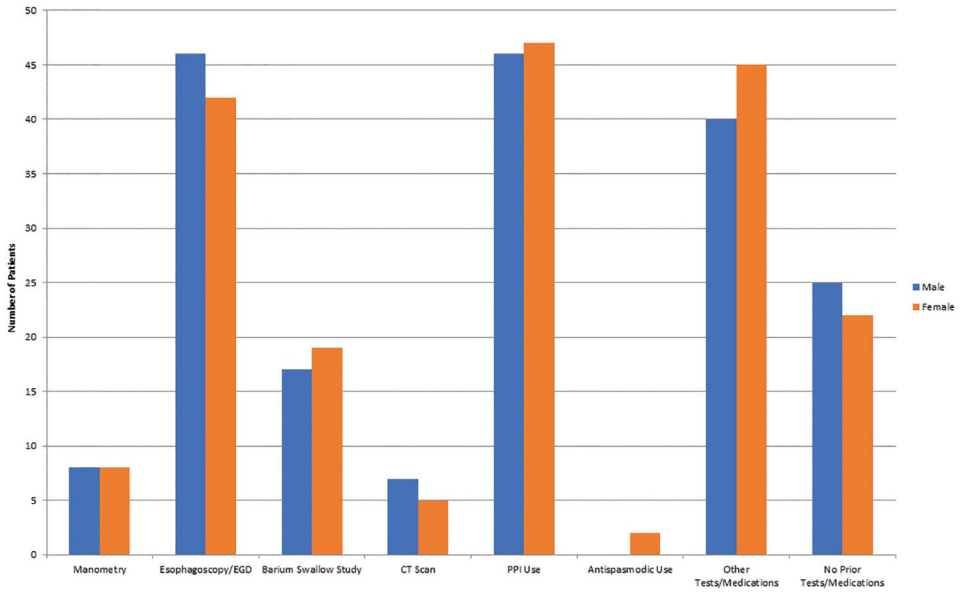


**Figure 1.** Prior tests and treatments that patients underwent before presentation.

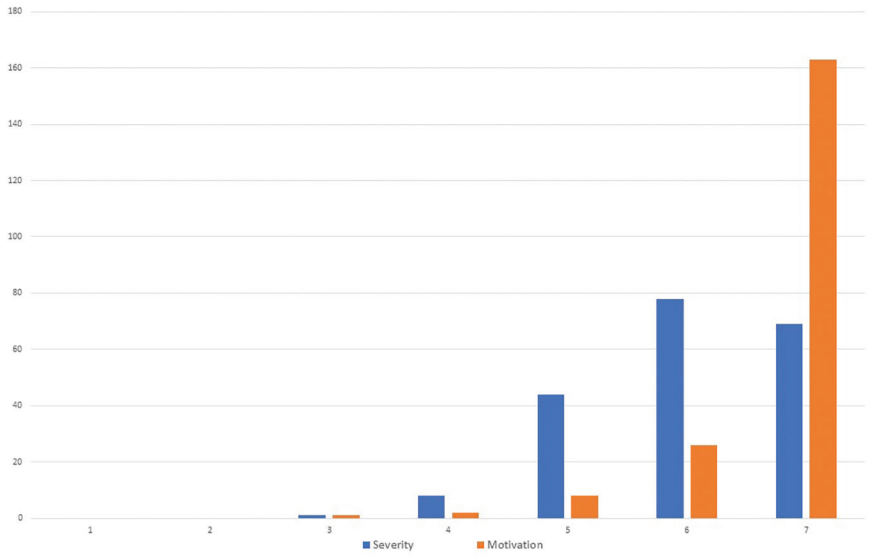


**Figure 2.** Patient perception of severity of symptoms and motivation to seek out treatment on a 7-point maximum-severity scale included in their intake questionnaires.

modest reduction of the cardinal symptoms of R-CPD. Three patients (1.5%) became able to burp, but it was limited, as was the reduction of other symptoms.

The 1 patient who did not experience postoperative relief was noted to have swelling intraoperatively and postoperatively, with noted greater and longer-lasting dysphagia than typical. However, besides this, he had no other complaints, and so he managed his swallowing by following solid food with liquids, and this gradually improved over the course of the week.

For those 199 patients who experienced any degree of relief, 159 patients (79.9%) maintained a satisfactory ability to burp after a minimum of 6 months (range, 6-52 months; average, 19.6 months; **Figure 3**). Of those 40 patients (20.1%) who did not maintain the ability, all patients began to lose their ability to burp within 4 months after treatment. Symptoms started to worsen as early as 2 weeks after surgery in the earliest of patients, with most patients stating they started to notice worsening between 2 and 3 months after injection. The mean and median age of those who lost their response were 39.2 and 38 years of age as compared with the mean and median age of those who kept their response of 28.0 and 26 years of age. Sixteen patients underwent retreatment, increasing dosage by at least 25 units, which again relieved symptoms: 12 patients underwent a second injection, 1 patient underwent 3 subsequent

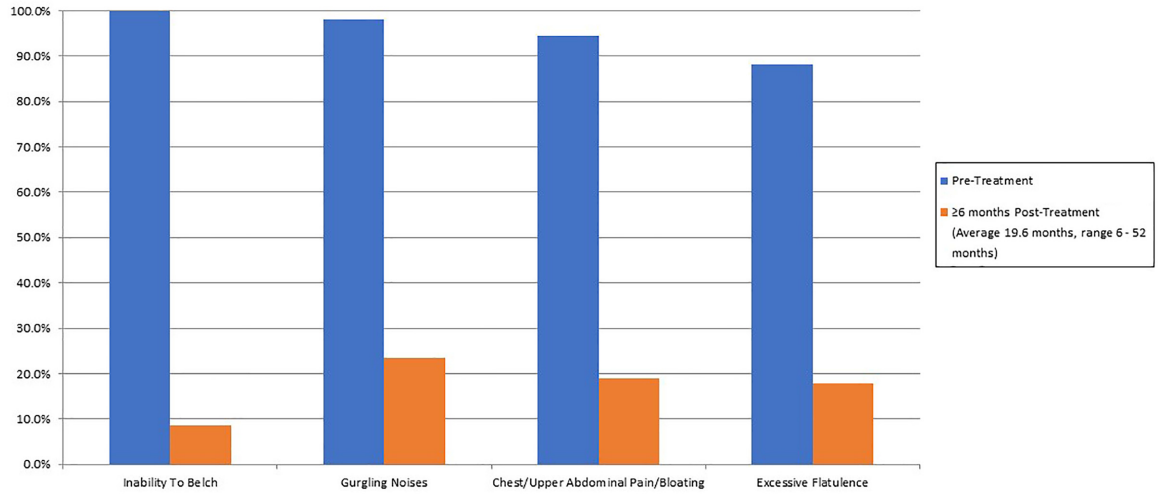


**Figure 3.** Prevalence of symptoms associated with retrograde cricopharyngeus dysfunction, at diagnosis and at 6 months posttreatment.

injections, and 3 patients elected to proceed with endoscopic partial myotomy instead of repeat injection. Of the 12 patients who underwent a second injection, 8 experienced long-term relief after the second injection. Of the patients who underwent partial myotomy, follow-up is currently ongoing, but 1 patient had good relief, 1 patient had relief but then recurrence, and 1 patient is currently lost to follow-up.

No patient reported a major complication at the botulinum toxin injection site or from the botulinum toxin injection itself. Complications related to esophagoscopy were noted in 3 patients. One patient had a small chip in a tooth, and 1 patient noted months of upper incisor tooth pain from esophagoscopy. Another patient had a superficial scrape of the posterior pharyngeal wall due to ''strenuous esophagoscopy'' necessitated by extremely difficult anatomy and proceeded to transient cellulitis of the posterior pharyngeal wall that resolved quickly upon treatment with antibiotics. Finally, 1 patient had a complication related to anesthesia, as the patient developed laryngospasm on emergence from anesthesia and subsequent presumed postobstructive pulmonary edema based on the production of pink frothy sputum and early postoperative hypoxia to the low 90s. The patient was carefully monitored and treated conservatively until his oxygen saturation improved without need for admission.

## Discussion

R-CRD is a recently described disorder by Bastian and Smithson[1] that appears to result from abnormal retrograde function of the cricopharyngeus muscle, which will not relax to permit eructation and, in some patients, vomiting. This results in a significant impact on the patient's quality of life, as demonstrated by the ratings of severity and motivation of the patients to solve this issue. Unfortunately, this disorder remains little known in the medical community, with very few publications to address this issue to date. The first mention of the symptoms of what can now be recognized as this disorder was in a case report in 1987, which described a patient with an inability to belch, chest pain, and gurgling noises, but no etiology or treatment was proposed.[2] Two other individual case reports were found in the literature, each describing an individual patient with the inability to belch, abdominal pain/bloating, and gurgling noises.[3,4] In these studies, manometry revealed an absence of relaxation of the upper esophageal sphincter (UES), but again, no underlying etiology or treatment protocols were suggested or trialed. Adding a case series of 51 patients to these earlier reports, Bastian and Smithson[1] were the first to codify all of the syndromic criteria and introduce Botox injection into the cricopharyngeus muscle as a potent confirmatory diagnostic test and universally successful treatment wrapped together. A literature search since that time has revealed only 1 additional article on this topic, which was again a case report describing a similar patient, and again, without successful treatment, suggesting that R-CPD remains unknown to the medical community.[5]

As proposed previously and confirmed by Bastian Voice Institute's additional 149 patients reported here, a strong preliminary diagnosis appears to be possible from the R-CPD syndrome on its own. That is, despite the fact that most patients had undergone tests and treatments elsewhere, none arrived at Bastian Voice Institute with the correct diagnosis nor had any found treatments recommended elsewhere helpful. After matching them with the syndrome, this means the diagnosis seems to have been validated by the combined diagnostic test/treatment with botulinum toxin. In fact, 99% of patients were able to burp and 95% experienced major relief of symptoms. Again, this further experience has the effect of validating the utility of preliminary syndromic diagnosis and suggesting that, as the second step, botulinum toxin injection into the cricopharyngeus muscle is arguably the only confirmatory diagnostic test needed.

Interestingly, we have found that approximately 80% of patients maintain the ability to burp beyond the expected duration of action of botulinum toxin. The authors do not have a certain explanation but speculate that this may be a result of ''retraining'' of the cricopharyngeus muscle, as no

other explanation can account for the resolution of a lifetime of dysfunction of the sphincter by a single injection of a medication whose effect is not permanent. In addition, the fact that those who lost the ability to belch began to do so by 4 months at the latest supports the idea that the botulinum toxin duration of action in the cricopharyngeus muscle might be approximately 4 months, as it is in many other muscles.

For the approximately 5% of patients who gained some ability to burp but did not experience significant improvement, we hypothesize that this is a result of either a need for a larger dose in these specific patients because of their relative insensitivity or that it was a targeting issue. It is well known that the dose of botulinum toxin needed can vary widely in individuals with other conditions such as spasmodic dysphonia, and so it is possible that those who did not have as robust a response were less sensitive to the medication.[6-8] This is further anecdotally suggested by the fact that one of the patients with minimal response had previously been treated with botulinum toxin for a separate condition and that the series of injections gradually had a decreasing effect despite increasing dose. Alternatively, it is also possible that the accuracy of targeting of the muscle plays a role in response, as a less perfectly targeted injection could result in a smaller intramuscular dose, resulting in less relief of symptoms.

It is hypothesized that the 1 patient who did not experience relief at all possibly developed a small hematoma within the UES based on our having noticed intraoperative swelling immediately after injection. We were not able to verify this explanation in the man, who traveled a long distance for treatment. Anecdotally, he was also noted to have a hypertrophied cricopharyngeus muscle intraoperatively, which also could have contributed, or it is possible his injection was superficial instead of in the muscle itself.

Additional studies in a larger population of patients are required to further understand the etiology of R-CPD and possibly to predict which patients would fall into the 20% of patients who lose their ability to burp when the botulinum toxin wears off. Lang et al[9] have previously investigated the role of esophageal distention in various esophageal reflexes in cats, including a contractile response to the cricopharyngeus muscle. While dysfunction of this reflex could be a possible cause of this syndrome, further work will need to be performed to elucidate the exact etiology.[9]

In addition, further study is required to create and validate a patient-reported outcome measure for the symptoms of R-CPD and to reassess the severity of symptoms postoperatively, which would assist in the assessment of outcomes for future studies. We plan to perform a future study to evaluate whether difficulty in muscle visualization due to difficult anatomy, or muscle characteristics such as bulk and reduced compressibility suggesting fibrosis, or dose might correlate with permanence of result. Finally, randomized controlled trials will be needed to validate the role of the injection of botulinum toxin for the treatment of this condition.

A primary limitation of this study is its retrospective nature. In addition, the patients who present with this disorder have thus far been self-referred, and thus this likely selects for those whose symptoms are more severe. There was also no control group. This possible selection of only the most severe R-CPD patients in turn may explain why so many of them have described their response to botulinum toxin injection as ''life changing.''

## Conclusion

Retrograde cricopharyngeus dysfunction is a recently described disorder resulting from apparent failure of the cricopharyngeus muscle to relax to permit belching and sometimes vomiting. Based on our experience with 200 patients, syndromic criteria provide a powerful diagnosis. When treated with botulinum toxin injection to the cricopharyngeus muscle, the utility of syndromic diagnosis was validated in 99% of our patients. Of these patients, 79.9% had relief lasting more than 6 months. Thus, we propose that for syndromically diagnosed R-CPD, botulinum toxin injection into the cricopharyngeus muscle is a safe and effective validating diagnostic test and treatment.

### Author Contributions

**Rebecca C. Hoesli**, substantial contributions to conception and design of work, acquisition, analysis, and interpretation of data, drafting and critically revising work, final approval of work, and agreement to be accountable; **Melissa L. Wingo**, substantial contributions to acquisition, analysis, and interpretation of data, drafting and revision work, final approval of work, and agreement to be accountable; **Robert W. Bastian**, substantial contribution to conception and design of work, interpretation of work, critical revision of work, final approval of work, and agreement to be accountable.

### Disclosures

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