First Bite Syndrome: Our Experience With Intraparotid Injections With Botulinum Toxin Type A

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Objectives/Hypothesis: First bite syndrome is the sudden onset of acute and severe pain in the parotid region at the initiation of mastication. Although it generally lasts less than a minute, it is disabling for these individuals and leads to a fear of oral intake. It is typically seen after parapharyngeal or deep parotid space surgery. Intraparotid injection of botulinum toxin A (BTA) has been suggested as a treatment for this condition, but there is little supporting literature to this effect. The purpose of this study is to document our experience using this treatment method for first bite syndrome.

Study Design: Retrospective case review.

Methods: Five patients with first bite syndrome, developed after parapharyngeal space surgery, were treated by multi-site injection of BTA into the parotid gland. Between 17.5 and 50 total U of BTA were injected into four or more sites in the parotid region. The patients were then followed up every 4 months.

Results: Three of five patients reported a significant improvement in symptoms at the 4-month follow-up visit, although complete resolution was not reported. One patient reported only moderate improvement, and despite two series of injections there was no improvement in one patient, leading us to question our initial diagnosis.

Conclusions: Unilateral BTA injection into the affected parotid gland produces a decrease in the severity of symptoms. It is a safe and viable noninvasive treatment for this difficult to treat condition and may lead to permanent resolution of symptoms in some patients.

Key Words: Quality of life, salivary glands.

Level of Evidence: 4

INTRODUCTION

First bite syndrome is a complication of parapharyngeal space and deep parotid surgery that presents as intense pain in the parotid region and jaw with radiation to the ear upon initiation of mastication. The pain characteristically lasts a few seconds, improves with each subsequent bite, and is at its worst with the first meal of the day. It can have a significant effect on quality of life and physical health of patients, sometimes even leading to avoidance of eating. A previous survey estimated the incidence of first bite syndrome in up to 18% of patients after parapharyngeal space surgery.1

The parapharyngeal space is richly supplied with a complex neurovascular anatomy. Netterville initially proposed that first bite syndrome is derived from damage to the cervical sympathetic system with loss of sympathetic innervations to the parotid gland, resulting in supersensitivity of the sympathetic receptors that control myoepithelial cells.2 An intense response by the myoepithelial cells is elicited on cross-stimulation of parasympathetic neurotransmitters (such as acetylcholine) released by chewing and biting.

A number of different treatment mechanisms have been studied with limited effect. For example, dietary modification with limitation of sialogogues has been found to be completely ineffective.2,3 Similarly, pharmacologic treatments have been unclear in their effect. Some data suggest that pregabalin and carbamazepine might be safe and effective, but this is still incompletely studied.4–6 Radiation therapy, despite the invasiveness, has proven to have complete resolution within 1 year but is a high-morbidity therapy.7,8 Finally, among proposed surgical treatment, tympanic neurectomy and auriculotemporal bone resection are both high risk, as they involve surgery and have not been shown to be effective.9,10

There has been a recent movement to find a safe and effective alternative to these treatments. Botulinum toxin type A (BTA) prevents the release of acetylcholine in synapses. BTA has been widely applicable in the field of ear/nose/throat and provides a useful tool in the treatment of spasmodic dysphonia, autonomic dysfunction, Frey syndrome, hemifacial spasm, and hyperfunctional lines. When administered in the parotid gland, BTA injection can result in selective blockade of parasympathetic neurotransmitters, which then decreases the cross-stimulation of sympathetic receptors on
myoepithelial cells in the area. In recent years, this theory has gained popularity, but there is a dearth of literature to provide safety, dosing, and efficacy results. On survey of the current literature, there are only three other articles to describe use of BTA for first bite syndrome. The first case report by Ali et al. in 2008 describes a patient who experienced complete resolution of symptoms up to 10 weeks after injection with 75 U of BTA.9 Similarly, articles by Lee et al. in 200911 and Sims et al. in 20133 have shown injections of BTA to decrease symptoms for up to 4 months. We describe our experience with intraparotid injections of BTA for the treatment of first bite syndrome.

MATERIALS AND METHODS

Patients who had undergone parapharyngeal space surgery and were complaining of facial pain on mastication on postoperative follow-up were identified in the Department of Head and Neck Surgery over a 3-year period. Disease burden requiring treatment was based upon the symptoms related by patients; this included multiple postoperative visits with the physician during which the patient reported facial pain upon first bite, fear and anxiety with eating, and subjective impairment in quality of life. Patients were initially given reassurance and followed closely. However, if symptoms persisted beyond 4 to 6 months after surgery, BTA injections were offered. Five patients (three women and two men) with first bite syndrome that developed after head and neck surgery were selected per internal review board–approved protocol and treated by injection of BTA into the parotid gland using ultrasound guidance. The diagnoses of the patients are summarized in Table I.

All patients were informed of the details of therapy and its possible side effects and gave their written consent to undergo treatment. Each patient had undergone surgeries performed for benign tumors, the resection of which involved dissection within the parapharyngeal space carried out posteriorly toward the sympathetic chain. No patient had preoperative findings of Horner syndrome or cranial nerve deficits. The surgeries performed included parotid/parapharyngeal space pleomorphic adenoma in two patients, resection of carotid body tumor in one patient, and resection of skull base/temporomandibular joint giant cell tumor in one patient. The clinical symptoms of first bite syndrome were present for 4 to 6 months prior to first injection.

Injection Technique

All patients received local injection of BTA (Allergan, Irvine, CA) reconstituted with 0.9% sodium chloride solution into multiple locations in the parotid gland under sonographic control. The affected parotid gland received between 10 and 40 U of toxin fractionated into between two and seven doses, injected at two or more sites. The injection amount depended on the severity of symptoms related by the patient. Similarly, the number of sites of injection depended on the patient-reported site of facial pain. The sites within the parotid gland were selected based on localization by the patient of where they experienced severe pain (Fig. 1). The injections, which were administered without local anesthesia, were well tolerated by all patients.

Pain Assessment

At each pretreatment visit, patients were asked to rate their pain on a scale of 0 to 10 (10 being the most severe) without a visual analog scale, and at each subsequent visit this rating was repeated. The rating was verified by both the medical assistant and the physician seeing the patient. Patients were asked to visit within 4 months for evaluation. At their 4-month

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**TABLE I.**

Description of Patient Characteristics, Diagnoses, and Time to Treatment.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, yr</th>
<th>Diagnosis</th>
<th>Time Before First Injection, mo</th>
<th>Other Complications of Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>77</td>
<td>Pleomorphic adenoma</td>
<td>4</td>
<td>Cheek numbness</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>46</td>
<td>Giant cell tumor, TMJ</td>
<td>4</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>67</td>
<td>Pleomorphic adenoma</td>
<td>6</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>49</td>
<td>Carotid body tumor</td>
<td>4</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>29</td>
<td>Carotid body tumor</td>
<td>6</td>
<td>None</td>
</tr>
</tbody>
</table>

F = female; M = male; TMJ = temporomandibular joint.

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Fig. 1. Intraparotid Botox injections mapped out using the anatomy of the parotid gland and patient localization of pain complaints. Each dot represents a site of injection. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]
visit, depending on the severity of symptoms, they would receive repeat dosing until complete resolution of symptoms.

RESULTS

Three of five patients reported significant improvement in symptoms from severe (9–10) to moderate (4–6) at the 4-month follow-up visit, an average decrease of 4 to 5 pain grades. One patient report moderate improvement, which was defined by a decrease of 1 to 2 pain grades after injection. The improvement in symptoms was based on the subjective pain scales related by the patient at each visit, by reduction of symptoms to a level deemed manageable by the patients, and also by patient satisfaction with quality of life improvement. No clinical correlation was observed between these outcomes. The last patient reported no improvement at all. None of the patients reported complete resolution of symptoms after the first injection.

It should be noted that by the 4-month follow-up visit, symptoms were beginning to recur and four patients did end up receiving repeat BTA injections of the same dosing. Patients received between one and four repeat injections, with 4 months between injections. The patients stated that their pain continued to be significantly improved for a number of months after the injections but would begin to recur with the same intensity within the 4-month period, requiring repeat injections. This process continued until the complete resolution of the symptoms. Treatment duration before resolution was on average 16 to 17 months (range = 10–28 months) after first injection. The patient who did not report improvement upon initial injection continued to report no change in symptoms, leading us to question our initial diagnosis. Our experience with BTA injections is summarized in Table II.

DISCUSSION

This study reports on our experience with intraparotid BTA injections for treatment of symptoms of first bite syndrome, which is the experience of severe pain upon initiation of mastication following parapharyngeal space surgery. First bite syndrome is thought to be caused by damage to the sympathetic chain, causing loss of sympathetic activity to the parotid gland. As such, sympathetic receptors are hypersensitive to neurotransmitters such as acetylcholine, which are released by the parasympathetic nerve fibers upon salivation or chewing. Thus, upon initiation of mastication, cross-stimulation of the receptors causes severe contraction of myoepithelial fibers and subsequent pain. First bite syndrome can be severe enough to hinder a patient’s quality of life and ability to eat.

Unfortunately, the management of first bite syndrome has proven elusive.

Initial treatment usually involves dietary modifications with avoidance of sialogogues or nonsteroidal anti-inflammatory drugs, but these have proven completely ineffective. Pharmacologic therapies have been extended to the use of gabapentin, pregabalin, and carbamazepine. Of these, gabapentin has proven only moderately effective, showing a decreased duration of symptoms but continued severity. Pregabalin and carbamazepine have been effective but incompletely studied. Alternatively, radiation therapy has proven itself effective, with complete resolution of symptoms within 7 to 10 months. However, radiation has multiple side effects and high comparative morbidity. Finally, surgical treatments such as tympanic neurectomy and auriculotemporal nerve resection are unsuccessful as well as invasive.

The BTA injection into the affected parotid gland is a new, safe, and effective method in the management of first bite syndrome. The BTA injection into the parotid gland blocks acetylcholine, and this blockade of neurotransmitters decreases the intense myoepithelial contractions derived from cross-stimulation of sympathetic receptors, thus relieving the pain symptoms experienced on initiation of mastication. Relatively few reports exist regarding the use of BTA for this novel application, much less regarding dosing, safety, and efficacy. However, no side effects were reported by this series of patients. Moreover, previous US Food and Drug Administration reports have validated the safety of intraparotid injections of Botox for sialorrhea; it follows that the excellent safety profile likely extends to this novel application. Further studies must still be executed, but this case series provides preliminary information on these topics.

Previous papers have established that use of intraparotid BTA significantly improves and can resolve symptoms of first bite syndrome. In the Ali et al. study as well as the Sims et al. study, doses of 75 U were used to alleviate symptoms, focusing on the areas of greatest first bite pain, usually in a single injection. Conversely, the Lee et al. study used 33 U divided into 11 U at three separate sites. In our experience, we

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**TABLE II.**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Preinjection Pain</th>
<th>Postinjection Pain</th>
<th>Total Units/No. of Sites</th>
<th>No. of Repeat Injections</th>
<th>Duration of Treatment Before Resolution, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8–9</td>
<td>4–5</td>
<td>22.5 U/7 sites</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>6–9</td>
<td>4–5</td>
<td>20 U/4 sites</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>9–10</td>
<td>8–9</td>
<td>40 U/4 sites</td>
<td>2</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>6–9</td>
<td>6–9</td>
<td>10 U/2 sites</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>9–10</td>
<td>4–5</td>
<td>40 U/4 sites</td>
<td>3</td>
<td>16</td>
</tr>
</tbody>
</table>

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consistently performed multisite injections (between two and seven sites) with lower total doses (between 22.5 and 40 U) with significant improvement in symptoms. This was done because the limited literature has shown that despite the effectiveness of 75 U, it also results in marked and persistent pain. Thus, the optimal effective dosing of BTA for first bite has yet to be determined.

Also interestingly, our results compare to previous studies noting that while symptoms do improve/resolve, the effect lasts until about 4 months, when symptoms recur with the initial severity. This is due to the depletion of BTA effect. We managed this by repeating injections every 4 months until resolution of symptoms. We used the same dosing each time, as this seemed to improve symptoms to a manageable degree.

It has been noted that symptoms of first bite syndrome can improve over time and can even self-resolve. It is likely that even patients who needed multiple injections would experience this improvement eventually despite severe, recurring symptoms, and symptoms would finally resolve. Thus, the use of BTA can be a safe, noninvasive, and effective temporizing measurement to alleviate symptoms of first bite syndrome. Further studies are needed to optimize the treatment protocol with respect to first bite syndrome.

CONCLUSION

First bite is a painful complication of parapharyngeal space surgery, involving the cross-stimulation of sympathetic receptors and subsequent intense myoepithelial contraction by neurotransmitters such as acetylcholine. Intraparotid injection of BTA is thought to block acetylcholine, suggesting that this could prove an effective treatment for first bite syndrome. Our experience shows that intraparotid BTA injections produce a decrease in the severity of symptoms; it should be considered a noninvasive and effective option in the treatment of this difficult to treat condition. Future studies should be carried out to optimize the dosing protocol for the specific treatment of first bite syndrome.

BIBLIOGRAPHY