Review Article

Botulinum toxin A for the treatment of first bite syndrome—a systematic review

Noah E. Shaikh[1]^, Haseeb A. Jafary[2]^, John W. Behnke[1]^, Meghan T. Turner[1]^

[1]Department of Otolaryngology-Head and Neck Surgery, West Virginia University Health Sciences Center, Morgantown, WV, USA; [2]Marshall University School of Medicine, Huntington, WV, USA

Contributions: (I) Conception and design: NE Shaikh, MT Turner; (II) Administrative support: MT Turner; (III) Provision of study materials or patients: NE Shaikh, HA Jafary; (IV) Collection and assembly of data: NE Shaikh, HA Jafary; (V) Data analysis and interpretation: NE Shaikh, HA Jafary, JW Behnke; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Meghan T. Turner, MD. Department of Otolaryngology-Head and Neck Surgery, West Virginia University Health Sciences Center, PO Box 9200, 4525 HSN, Morgantown, WV 26506-9200, USA. Email: meghan.turner@hsc.wvu.edu.

Background: First bite syndrome (FBS) is a rare post-surgical complication resulting in peri-parotid pain after the first bite of meals. Intra-parotid Botulinum toxin A may offer relief for these symptoms. There is no consensus on the optimal dosage, timing to symptom improvement, need for repeat injections, and safety of this treatment. The objective of this systematic review was to assess the efficacy and safety of intra-parotid Botulinum toxin A injection in treating FBS.

Methods: The MEDLINE, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar were searched from the inception until July 2020. Case reports, case series, prospective and retrospective trials in which patients with post-surgical FBS were treated with intra-parotid botulinum toxin A injection were included. The primary outcome was improvement of FBS symptoms. Secondary outcomes were time to symptom improvement and complications. Risk of bias was assessed with National Institute of Health (NIH) Quality Assessment Tools.

Results: Search results yielded 41 studies. Thirty-three articles were excluded after screening titles, abstracts, and full texts, yielding eight studies, from which 22 patients were included. No studies included a control. All studies were of lower quality and had at least moderate risk of bias. The initial botulinum toxin A injection dose ranged from 10–75 U. Time from surgical treatment to injection ranged from 1 month to 3 years. Seven studies, containing 17 patients, reported individual patient outcomes. Clinical improvement was reported in 16 patients lasting between 1–30 months post injection. Eight of 8 (100%) patients receiving at least 40 U botulinum toxin A had symptom improvement. Ten of 22 (45.5%) patients received a second botulinum toxin A injection due to return of pain at a mean of 3.8 months after the first injection. Seven of 22 (38.1%) patients had complete symptom resolution at a mean of 12.1 months. There were no reported injection complications, including: facial paralysis, infection, injection site reaction, and allergic reaction.

Discussion: There are no controlled studies comparing intra-parotid botulinum toxin A to observation for FBS. However, botulinum toxin A appears to be a potentially safe, effective treatment.

Keywords: First bite syndrome (FBS); botulinum toxin A; botox; parotid; systematic review

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^ ORCID: Noah E. Shaikh, 0000-0002-4834-2769; Haseeb A. Jafary, 0000-0003-2951-5801; John W. Behnke, 0000-0002-6359-7700; Meghan T. Turner, 0000-0001-8621-6168.

Introduction

First bite syndrome (FBS) is a rare, often temporary, postoperative pain syndrome that is characterized by pain in the parotid region with the first bite of a meal that diminishes in severity with each succeeding bite (1-3). It is an iatrogenic complication of surgery involving the parotid gland, parapharyngeal space (PPS), or infratemporal fossa (ITF) (3-12). The pathophysiologic mechanism was first described by Netterville *et al.* (4), and is caused by damage to the sympathetic branches innervating the parotid gland during surgery and development of sequent denervation hypersensitivity from unopposed parasympathetic contractions of the salivary gland myoepithelial cells that elicit pain during onset of gustatory salivation (1,4,13).

Botulinum toxin is produced by the anaerobic bacteria *Clostridium botulinum* (14). The use of botulinum toxin prevents acetylcholine release from the synapse via cleavage of SNARE proteins, which prevents acetylcholine containing vesicles from binding to the intracellular membrane. The resulting blockade of acetylcholine release leads to a decrease in the parotid gland's physiologic secretion of saliva (14,15). Injection of botulinum toxin type A (BTA) for the treatment of FBS has been hypothesized to induce medical parasympathetic nerve blockade at the myoepithelial neuromuscular junction and to therefore, decrease pain during parotid gland salivation (16-18).

While FBS may spontaneously resolve in 6–20% of patients (2,5,19,20) and partially improve in 69–82% of patients (2,5,20); 15–18% of patients may develop undiminished, chronic pain (5,19). The time to spontaneous resolution has been reported to be from 1–18 months (10,20-24). Prior medical treatments aimed at FBS include carbamazepine with and without concomitant amitriptyline (19-21,25,26), nonsteroidal anti-inflammatory drugs (20,27), opioids (28), hyoscine (28), gabapentin (19,21), pregabalin (19,29), and local anesthetics (16,19,21,28). Procedural treatments such as acupuncture (16), tympanic neurectomies (16,20), radiation (19,27), tumor remnant excision (30-33), and parasympathetic removal have also been attempted. These medical and surgical treatments have yielded limited therapeutic responses in patients (2,16,19-21,25-33).

Botulinum toxin is widely used in many fields of medicine today to treat various conditions pertaining to nerve and muscle hyperactivity, including auriculotemporal syndrome (Frey syndrome), strabismus, rhytids, focal dystonia, hemifacial spasms, spastic muscular disorders, headaches, hypersalivation, and hyperhidrosis (34-38). Ali *et al.* (16), reported the first use of BTA injection for treatment of FBS in a 53-year-old patient who had undergone several surgical resections for a right neck lymphangioma. The patient had trialed multiple treatments, including tympanic neurectomy, acupuncture, and narcotics, for the treatment of FBS with limited success. She received a BTA injection and had near complete resolution of symptoms within 2 days. Since this first successful treatment report, multiple further studies (39-45) have investigated the use of BTA for surgically caused FBS. Additionally, there is evidence for its benefit in idiopathic FBS (46). No consensus is present on the optimal dosage, timing of repeat injections, timing to symptom improvement, or safety for this treatment option. The aim of this systematic review was to assess the dosing in units, success of injection, the average time to improvement of FBS and complications after intra-parotid BTA in the literature. We present the following article in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting checklist (47) (available at https://gs.amegroups.com/article/view/10.21037/gs-22-112/rc).

Methods

Research Questions and analytic framework

Our systematic review was designed to assess whether intra-parotid injection of BTA is an effective treatment of FBS. Our secondary objective was to assess dosages used for FBS, time to improvement of symptoms after BTA injection and complications of treatment. *Table 1* presents the PICO question.

Protocol and registration

We had registered our systematic review with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42020201836.

Ethical considerations

This study is a systematic review of literature and does not require institutional review board (IRB) approval.

Eligibility criteria

Studies of patients with FBS of surgical etiology receiving treatment with intra-parotid BTA injection were included.

Table 1 PICO: inclusion and exclusion criteria

PICO elements	Inclusion criteria	Exclusion criteria
Population	FBS secondary to surgery	FBS secondary to non-surgical etiology
	All ages	No age restriction
	Human studies	Animal studies
	All languages	Cadaver studies
	All publication types	
Intervention	Intra-parotid botulinum toxin injection	Not utilizing botulinum treatment for FBS
		Not discussing treatment methodology or dosage
Comparison	Patients not receiving intra-parotid botulinum toxin or patients receiving intra-parotid saline injection	NA
Outcome	Resolution of symptoms of FBS	NA
	Time to improvement of FBS	

PICO, Population, Intervention, Comparison, Outcome; FBS, first bite syndrome; NA, not applicable.

Table 2 Database search criteria

Database searched	Search terms
PubMed/MEDLINE	(first bite syndrome) AND (botu* OR botox)
Embase	('first bite syndrome'/exp OR 'first bite syndrome' OR (first AND ('bite'/exp OR bite) AND ('syndrome'/exp OR syndrome))) AND botulinum
Cochrane Library	(first bite syndrome) AND (botu* OR botox)
Google Scholar	(first bite syndrome) AND (botulinum OR botox)

*, this symbol is used at the root of a word to find multiple endings.

All ages, genders, study methodologies, geographies, languages, publication types were included. Additionally, patients who had failed observation or medical or surgical treatments of FBS prior to intra-parotid BTA injection were included. All surgical approaches and surgical indications were included. Randomized and non-randomized control trials, prospective studies, retrospective studies, case series and case reports were eligible for inclusion. Exclusion criteria included: FBS due to non-surgical etiology (including idiopathic and oncogenic origin), animal studies, and cadaver studies. Studies in which intra-parotid BTA was administered but treatment dosage, etiology or outcomes were not reported were also excluded.

Data source and search strategy

An electronic search of the MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar databases was performed from time of inception to July 1, 2020. A table with the specific search terms used for the search for each database is included in *Table 2*.

Study selection and data extraction

Studies were screened by title, abstract, and full text by two independent reviewers (NS and HJ). Data extracted from each study included: study ID, study title, year of publication, study design, number of patients, age of patients, sex of patients, presence of tumor, pathology of tumor, surgical approach, botulinum toxin treatment strategy, number of repeated injections, timing of repeated injections, cause for repeat injections, improvement in symptoms, timing to improvement in symptoms, length of resolution of symptoms, length of follow-up, symptoms duration after surgery, resolution of symptoms, time to

resolution of symptoms, time to return of symptoms of significant intensity, injection technique, use of multi-site injection, and complications. Data extraction was performed by two independent reviewers (NS and HJ). At the beginning of data collection, an attempt was made to contact authors for full text article when only available as a poster or when a limited data set was presented (46,48,49).

Risk of bias and study quality assessment

The National Institute of Health (NIH) Quality Assessment Tools provides methodological frameworks for systematically assessing risk of bias in controlled and uncontrolled studies (50). While the NIH tool is not traditionally used to assess for bias, we used it as a proxy given the limitations provided by the types of studies included. The quality assessment tools for both before-after studies with no control group and case series studies were used as applicable for the studies included. These tools study multiple domains including objectivity, patient similarity, selection criteria, blinding, classification of interventions, missing data, measurement of outcomes, follow-up adequacy, and result clarity. Studies were assigned an overall score of risk of good, fair, or poor.

Results

Study selection

A total of 41 studies were identified from literature search. Twenty-eight studies remained after removal of duplicate studies. Twenty articles were excluded after reviewing the full text for reasons including: not treating with botulinum toxin, no report of treatment dose or treatment effects, patient did not have FBS, and non-surgical etiology of FBS. Eight studies were included in the final review, of which the poster only was available for one article (45). This poster contained all the necessary treatment details for the purposes of the review. However, an attempt was still made to retrieve the full-length manuscript for this poster with no response from the author. The literature search protocol for selection of eligible studies is presented as a PRISMA flow diagram in *Figure 1*.

Study characteristics

The eight studies included a total of 22 patients. There was one prospective study (42), two retrospective studies (40,41), one case series (39), and four case reports (16,43-45) included. The population size in the studies varied from one to five patients. All studies were single center studies. None of the studies had control data and only two patients demonstrated no improvement within the time frame assessed (41,42). As such, the results of this study are purely descriptive and not sufficient for meta-analysis.

Risk of bias in studies

All studies were determined to be of fair to poor quality. *Tables 3,4* present the assessments of study quality.

Results of individual studies

Nineteen patients developed FBS secondary to tumor excision requiring PPS dissection (16,39-42), one due to superficial parotidectomy (43), and two due to carotid endarterectomy (44,45). Three studies commented on the occurrence of FBS following external carotid artery (ECA) ligation, from which only three patients had ECA ligation (39,40,42). As expected, there were no cases of FBS following total parotidectomy. One study commented on sympathetic chain sacrifice, totaling five patients, of whom, three had sympathetic chain sacrifice (42). Four studies commented on the presence of Horner's syndrome, totaling 16 patients, of whom six had Horner's syndrome (16,40-42).

Six studies reported specifically the use of multi-site injection technique over 20 patients (16,39-43,45). Five studies reported specifically on the use of ultrasound-guided injection in 13 patients (16,40,41,43,45). None of the studies divided the research population into two separate treatment groups, one receiving BTA treatment and a control group not receiving BTA treatment. All studies were case series or case reports and were of low quality. The characteristics of the studies and patients are included in *Tables 5,6*.

Outcomes assessment

Sixteen of 17 patients with individual level data reported improvement in symptoms during the follow-up period, which ranged from 1–30 months (median, 6 months) post injection (16,39,41-45). One retrospective study, treating five patients, measured a mean improvement in symptoms across the cohort, but did not report individual level data (40). Two studies reported resolution of symptoms in seven patients (39,41). No study reported a complication from BTA injection.

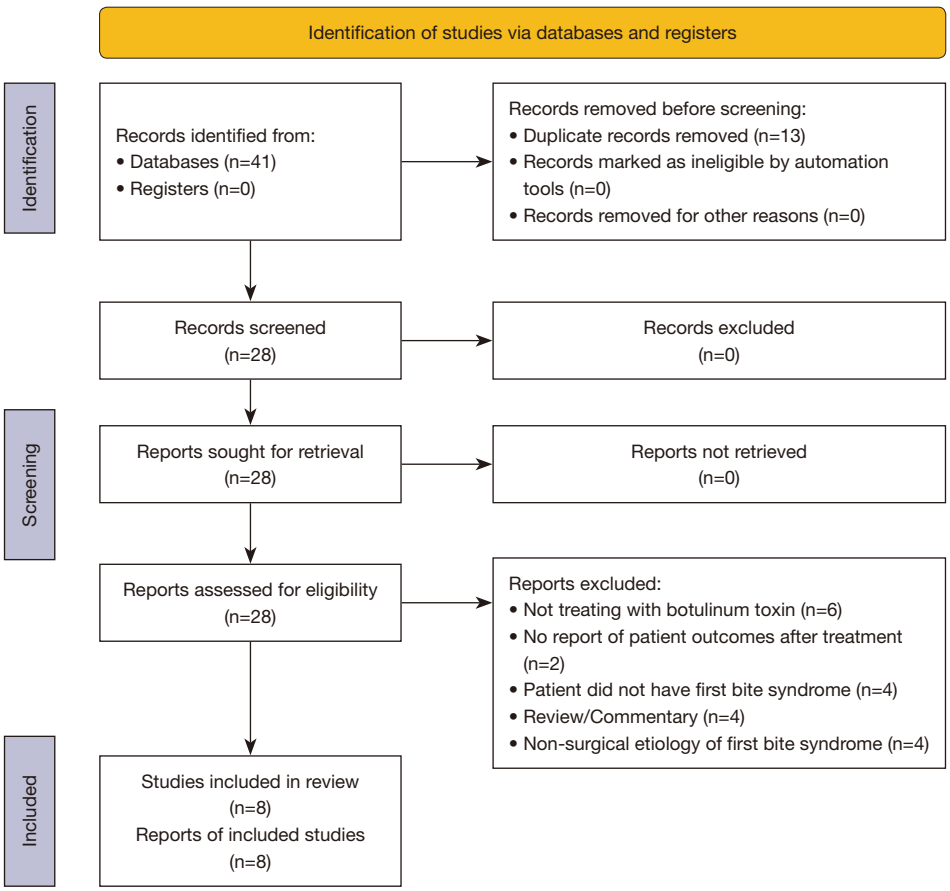

Figure 1 PRISMA flowchart of study selection process. From 41 initial studies identified with database search, 28 full-text articles were assessed for eligibility after screening by title and abstract and removal of duplicates. Eight studies were included in final systematic review. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Six studies assessed patients within 1 month of treatment (16,39,40,42-44), and four studies specifically mentioned individual patient's symptoms within 1 month of treatment of botulinum toxin (16,39,43,44). Six of 6 (100%) patients assessed within this time frame reported an improvement in symptoms. Seven studies assessed patients within 4 months of treatment (16,39-44), and five studies specifically mentioned individual patient's symptoms within 4 months of treatment of botulinum toxin (16,39,41,43,44). Ten of 11 (90.9%) patients assessed within this time frame reported an improvement in symptoms. Average time to improvement with non-scheduled assessments was 8.3 days. Four patients reported an improvement in symptoms within less than a week of injection (16,41). Eight of 8 (100%) of patients receiving at least 40 U of BTA (Botox) had improvement of symptoms at an average of 1.3 months (range, 1 day to 4 months) (16,39,41,43,44). Ten of 22 (45.5%) patients received second injection of botulinum toxin due to return of pain (39,41-43,45). The second injection was administered on average 3.8 months following the initial injection (range, 6 weeks to 7 months). Two patients received up to five injections of BTA (39,41), and the maximum cumulative injected dose was 160 U (41). In total, 31.8% of patients had complete resolution of symptoms at a mean of 12.1 months (range, 3 days to 28 months). *Table* 7 presents treatment dosing and schedule.

Discussion

In 1998, Netterville *et al.* (4), was the first to propose the mechanism of FBS after observing multiple patients develop FBS after removal of vagal paragangliomas who suffered

Table 3 Study Quality Assessment for before-after studies with no control group

Criteria	Costales-Marcos *et al.* (42)	Ghosh *et al.* (41)	Lee *et al.* (40)
Was the study question or objective clearly stated?	Y	Y	Y
Were eligibility/selection criteria for the study population prespecified and clearly described?	Y	Y	N
Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Y	Y	Y
Were all eligible participants that met the prespecified entry criteria enrolled?	CD	Y	CD
Was the sample size sufficiently large to provide confidence in the findings?	N	N	N
Was the test/service/intervention clearly described and delivered consistently across the study population?	N	Y	Y
Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Y	N	Y
Were the people assessing the outcomes blinded to the participants' exposures/interventions?	N	N	N
Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Y	Y	Y
Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Y	Y	Y
Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	N	Y	N
If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	NA	NA	NA
Quality rating (good, fair, or poor)	Fair	Fair	Fair

†, Study Quality Assessment Tool offered by the National Institute of Health (Source: National Heart, Lung, and Blood Institute; National Institute of Health; U.S. Department of Health and Human Services) (50). Y, yes; CD, cannot determine; N, no; NA, not applicable.

sympathetic denervation and unopposed parasympathetic innervation of parotid myoepithelial cells. In their study, eight out of nine patients with sympathetic chain injury (Horner's syndrome) developed FBS, characterized by pain during onset of oral intake. In 2002, Chiu *et al.* (20), reported a series of 12 patients that developed FBS after surgery of the PPS, in which six underwent ligation of the ECA and the other six patients had sacrifice of sympathetic chain with Horner's syndrome.

Linkov *et al.* (2), demonstrated three major variables that were significant predictors of FBS: sacrifice of the sympathetic chain, the extent of parotidectomy, and PPS dissection. Surgery involving the PPS, ITF, and deep lobe of the parotid significantly increased the risk of FBS, in addition to transcervical approach and sacrifice of the sympathetic chain or total parotidectomy. In their analysis, the three tumors most associated with development of FBS included schwannoma, paraganglioma, and pleomorphic adenoma. Additionally, female gender, and absence of prior radiation predisposed to FBS. They concluded that all 12 patients likely had loss of sympathetic innervation to the parotid gland. Multiple other studies have confirmed loss of sympathetic function to be associated with FBS including reports of pretreatment FBS in cases of ECA or sympathetic chain invasion by tumors, including mucoepidermoid carcinoma (31), adenoid cystic carcinoma (30), schwannoma (51), and synovial sarcoma (32).

This systematic review examines the potential of BTA to treat FBS resulting as a surgical complication. As previously discussed, while some patients develop resolution of symptoms within 1–18 months (5,10,19-23,27,52,53), up to 88% of patients continue to experience symptoms (2,5,19,24,53-55). Botulinum toxin has had multiple applications in otolaryngology, including dystonia of the

Table 4 Study Quality Assessment for case-series studies[†]

Criteria	Ali *et al.* (16)	Harirchian *et al.* (45)	Mikolajczak *et al.* (43)	Sims *et al.* (39)	Wang *et al.* (44)
Was the study question or objective clearly stated?	Y	N	Y	Y	N
Was the study population clearly and fully described, including a case definition?	Y	Y	Y	Y	Y
Were the cases consecutive?	NA	NA	NA	N	NA
Were the subjects comparable?	NA	NA	NA	N	NA
Was the intervention clearly described?	Y	Y	Y	Y	N
Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	N	N	N	N	N
Was the length of follow-up adequate?	Y	Y	Y	Y	N
Were the statistical methods well-described?	NA	NA	NA	NA	NA
Were the results well-described?	Y	Y	Y	Y	N
Quality rating (good, fair, or poor)	Fair	Fair	Fair	Fair	Poor

[†], Study Quality Assessment Tool offered by the National Institute of Health (Source: National Heart, Lung, and Blood Institute; National Institute of Health; U.S. Department of Health and Human Services) (50). Y, yes; NA, not applicable; N, no.

Table 5 Study characteristics

Reference	Year	Country/language	Design	Size	Sex [age]
Ali *et al.* (16)	2008	USA/English	Case report	1	F [53]
Costales-Marcos *et al.* (42)	2017	Spain/Spanish	Prospective case series	5	M, M, F, F, F; individual age not stated
Ghosh *et al.* (41)	2016	USA/English	Retrospective case series	5	M [46], M [29], F [77], F [67], F [49]
Harirchian *et al.* (45)	2011	USA/English	Case report	1	M [70]
Lee *et al.* (40)	2009	Korea/English	Retrospective case series	5	M [34], M [58], F [55], F [45], F [38]
Mikolajczak *et al.* (43)	2015	Germany/German	Case report	1	M [60]
Sims *et al.* (39)	2013	USA/English	Retrospective case series	3	M [67], F [44], F [34]
Wang *et al.* (44)	2013	New Zealand/English	Case report	1	M [75]

M, male; F, female.

larynx (56), laryngeal granulomas (57), laryngeal joint dislocation (58), cricopharyngeal spasm (57), posterior glottic synechiae (59), blepharospasm (60), hemifacial spasm (60), temporomandibular joint disorders (61), and oromandibular dystonia (60). BTA treatments generally last for 3 to 6 months (62,63).

While use of BTA is not commonly associated with many adverse side effects, the few that are present tend to be more transient in nature, such as pain in the injection site with local edema (64), erythema (65), and numbness (66). Generalized systemic side effects include headache (64), malaise (66), and nausea (66). Specifically reported complications from use in the head and neck include injection site bruising (65), local infection (65), and toxin spread locally or systemically with unintended paralysis (67,68), which can cause oculomotor disturbances (67), dysphagia (69,70), breathiness (71), and even delayed gall bladder emptying (72).

BTA is contraindicated in myasthenia gravis, Eaton-Lambert Syndrome, and concurrent use of agents that can

Table 6 Patient characteristics

Reference	Path	FBS cause	Previous treatments
Ali *et al.* (16)	Lymphangioma	PPS [1]	Tympanic neurectomy
Costales-Marcos *et al.* (42)	Schwannoma: 2, carotid paraganglioma: 2, vagal paraganglioma	PPS [5]	NA
Ghosh *et al.* (41)	Pleomorphic adenoma: 2, carotid body tumor:2, giant cell tumor	PPS [5]	NA
Harirchian *et al.* (45)	NA	Carotid endarterectomy [1]	Gabapentin
Lee *et al.* (40)	Carotid body tumor: 2, pleomorphic adenoma, sympathetic chain schwannoma, metastatic papillary cancer	PPS [5]	NA
Mikolajczak *et al.* (43)	Warthin tumor	Parotidectomy [1]	NA
Sims *et al.* (39)	Metastatic SCC, lymphatic malformation, AV malformation	PPS [3]	None
Wang *et al.* (44)	NA	Carotid endarterectomy [1]	NA

Patient number is in square brackets. SCC, squamous cell carcinoma; NA, not applicable; FBS, first bite syndrome; PPS, parapharyngeal space.

Table 7 Botulinum toxin A injection treatment dosing and schedule

Reference	Time from causative surgery to injection[†]	First injection dose[‡]	Injection technique	Time to improvement	Total dose	Total injections	Follow up times in months[§]
Ali *et al.* (16)	3 years	75 U [1]	USG, dose diluted in 2 mL NS, multi-site, focused on areas of most pain	2 days	75 U	1 [1]	2.5
Costales-Marcos *et al.* (42)	Mean and individual times not specified [2–17] months	30 U [5]	USG not specified, diluted in NS, multi-site, 1.5 cm anterior to tragus, 1 mL syringe, 25-G needle, without LA	6 months (4/5)	30–80 U	1 [2], 2 [3]	1, 3, 6
Ghosh *et al.* (41)	4.8 [4–6] months	10 U [1], 20 U [1], 22.5 U [1], 40 U [2]	USG, diluted in NS, multi-site, focused on areas of most pain	4 months (3/5)	20–160 U	1 [1], 2 [1], 4 [2], 5 [1]	4 [10–28]
Harirchian *et al.* (45)	Not specified	Dysport 280 U	USG, multi-site, superficial and deep lobes	Not specified	280 U Dysport + 50 U Botox	2 [1]	17
Lee *et al.* (40)	39.4 [22–60] months	33 U [5]	USG, diluted in NS, multi-site, without LA	1–3 months	33 U	1 [5]	1, 3, 6
Mikolajczak *et al.* (43)	3 months	35 U [1]	USG, dose diluted in 2 mL NS, multi-site	10 days	70 U	1 [1]	3
Sims *et al.* (39)	9.7 [4–18] months	75 U [3]	USG not specified, multi-site, focused on areas of most pain	1–4 days	75–200 U	1 [1], 3 [1], 5 [1]	[4–11.5]
Wang *et al.* (44)	Not specified	50 U [1]	USG not specified, multi-site not specified	1 month	50 U	1 [1]	1

Patient number is in square brackets. [†], time from causative surgery to first injection is provided as a mean, with the range in square brackets. If a study was a case report, only a single value is reported. [‡], all dosage units are reported for botulinum toxin A, Botox, unless otherwise specified. [§], follow up times provided as scheduled times, and range in square brackets. USG, ultrasound-guided; NS, normal saline; LA, local anesthesia.

interfere with neuromuscular junction (i.e., aminoglycosides, penicillamines, and quinines). After receiving BTA injections, patients are advised to stay upright for 3 to 4 hours, avoid strenuous activity, and refrain from undergoing any facial massage for 1 or 2 weeks because any increase in pressure or blood circulation may dislodge the toxin from the appropriate site. This generally does not last more than a few months and can resolve in a few weeks depending on the strength of the dose and the site of injection (34). Ultrasound can assist in precise injection (73).

We found eight relevant studies involving the treatment of FBS using BTA in a total of 22 patients. All treatments involved varying dosages of BTA and ranged from 10 to 75 U and were given at least once and up to five times in some patients (39,41). Most patients received BTA (Botox) as the only treatment for FBS; however, there was one patient that underwent two prior tympanic neurectomies (16) and one patient that received gabapentin, BTA (Dysport), and then BTA (Botox) (45). There have been other attempts to treat FBS with various medications, procedures, and acupuncture; however only around 12% of individuals experience complete resolution of symptoms (2,16,19-21,25-33).

This study has demonstrated promise of BTA in the improvement of symptoms in patients with FBS. From the limited data, it does appear that doses as low as 20 U can be effective (41). All patients receiving a dose of at least 40 U of BTA demonstrated improvement in symptoms (16,39,41,43,44). In certain patients, botulinum toxin appears to have rapid effect on symptom treatment, improving symptoms in as little as 1 day after treatment (39). Doses as high as 75 U and multiple sets of injections have been performed in a limited set of patients with no reported complications (16,39,41-43,45). Patients can have significant worsening of symptoms after treatment within a wide time frame between 6 weeks to 7 months after injection. Repeat injections can offer benefit to these patients. In our study, 31.8% of patients had complete resolution of their symptoms in a mean time of 12.1 months, compared to literature reports of persistent disease in up to 88% of patients (2).

The mechanism by which botulinum toxin injection improves FBS is unclear. Currently, there are no cellular or animal disease models of FBS, making the more basic study of the pathophysiology and pharmacologic mechanism of action difficult. However, we postulate BTA may improve resolution of the disease secondary to decreases in salivary gland weight, cholinergic output, secretory capacity, cellular size, and myoepithelial function after injection (74-76). Additionally, nerve growth factor (NGF) expression can be increased by BTA (77), which may lead to improved parotid gland sympathetic reinnervation (78). This may explain the potential long-term improvements some patients experience. Finally, since resolution occurs spontaneously (10,19-23), it may be that BTA serves as a bridge, treating the symptoms until time allows for natural recovery.

Our review has several important limitations. Very few patients in the literature have undergone botulinum toxin injection for the treatment of FBS (16,39-45). None of the included studies were randomized and all studies had at least a moderate risk of bias. None of the included studies had a control group at the start of the data collection for identifying patients who did or did not receive BTA. Most of the studies were small case series with a mixed patient population with varying surgical etiologies of FBS. Finally, there is no uniform subjective symptom score or objective measure of post injection symptom relief, so efficacy outcomes are purely based on subjective patient reported improvement or resolution.

The main objective of this study was to assess the efficacy and safety of BTA in the treatment of surgically induced FBS. However, due the limited data available in the literature as discussed above, we were not able to compare the outcomes of BTA to observation only. This is an important consideration given that FBS is known to improve or resolve spontaneously (10,19-23). Studies in this review utilized BTA from 2–60 months after development of FBS, which makes it difficult to parse the benefit of BTA over observation, especially in studies that started injections shortly after development of FBS. As such, observations about the efficacy of BTA over observation or placebo effect in the treatment of this syndrome cannot be made.

Implications

Currently, BTA is not used regularly to treat FBS. While it has demonstrated utility in a non-controlled context, a case-control or case cross-over trial might better assess the efficacy, time to improvement of symptoms and length of significant improvement in symptoms with the use of a standardized visual analog score (VAS).

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Footnote

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