Original Article

Local experience using botulinum toxin for the management of post-parotidectomy fistulas and recurrent parotitis

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Background: Botulinum toxin (BTx) reduces the production of saliva in salivary glands. Literature supporting the use of BTx in post-parotidectomy fistulas and recurrent parotitis is expanding, however use in Australia has been limited. We report our experience with BTx for the management of post-parotidectomy fistulas and recurrent parotitis.

Methods: Case series. Patients were injected with onabotulinumtoxinA into the affected salivary gland or residual salivary tissue.

Results: We present nine cases of parotid gland pathology successfully managed with BTx. Five patients were managed for post-parotidectomy fistulas, with four reporting complete resolution. Four patients were managed for recurrent parotitis, all reporting reduced symptoms. In those prescribed regular antibiotics, there was a reduction in use after BTx injection. Two patients had mild dry eyes after the injections, with no other side effects.

Conclusions: We advocate for the early use of BTx in the management of post-parotidectomy fistulas and recurrent parotitis based on available data and our nine cases.

Keywords: Parotid gland; parotitis; fistula; botulinum toxin (BTx); adult

Received: 30 October 2017; Accepted: 05 January 2018; Published: 15 January 2018.

doi: 10.21037/ajo.2018.01.05

View this article at: http://dx.doi.org/10.21037/ajo.2018.01.05

Introduction

The therapeutic indications for botulinum toxin (BTx) are expanding with literature advocating for its use in varied head and neck pathologies requiring a reduction in salivary gland output. The ability of the toxin to reduce the production of saliva was first described in research assessing the management of sialorrhea in patients with neurological conditions (1). This research initiated the novel use of BTx in the management of post-parotidectomy fistulas and recurrent parotitis as the reduction of salivary flow alleviates symptoms or allows healing.

Salivary fistulas after parotidectomy occur at a rate between 4% and 14% (2,3). The constant leak of saliva and associated increase in volume when eating can significantly impact a patient's quality of life (4). Treatment options aim to reduce the flow of saliva through the fistula to enable tissue healing (3). A variety of treatment modalities have been described in the literature including pressure dressings, anticholinergic medications, radiotherapy, suction drain insertion or completion of the parotidectomy (4-7). Unfortunately, these management options are limited by their efficacy, side effects or expose the patient to significant risks including facial nerve injury (6-8). In contrast, BTx has been described in the literature to be effective in reducing salivary flow to enable healing of the fistula, with the largest

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series documenting 10 cases (3,4,8-14)

Recurrent parotitis is repeated infections of the parotid gland that can be idiopathic or secondary to a variety of aetiologies, with many patients requiring regular antibiotics to manage the infections (15,16) Long term chronic and recurring inflammation can damage the structure of the salivary gland, leading to accumulation of saliva and an increased potential for further infections (17) Management of recurrent parotitis is directed at the aetiology, though typically involves a combination of antibiotics, oral steroids, sialagogues, analgesia and for particular causes including stones, sialendoscopy (18-20) However, some patients fail conservative management and require surgical intervention, subjecting them to significant risks. Efficacy of the conservative management options varies and the recurring need for antibiotics to manage the infective exacerbations increases the risk of antibiotic resistance. The evidence for BTx for the management of recurrent parotitis is limited, including a case series of 6 patients and individual case studies (12-14,17,21)

With limited support from the literature, the use of BTx for salivary gland pathology has been minimal in Australia. We aim to document our experience with BTx in the management of post-parotidectomy fistulas and recurrent parotitis to increase the awareness of this simple management option.

Methods

A retrospective chart review was performed and identified nine adult patients who had salivary gland pathology managed with onabotulinumtoxinA (Botox) between November 2013 and December 2015. At time of therapy, all patients gave informed consent, including the limited evidence for its use, theoretical rationale and potential adverse effects.

Medical records were reviewed to obtain: age, primary pathology, date of first and last injection of BTx, dose, number of treatments, location of injection and time to follow-up. All patients completed a follow up questionnaire to assess the change in symptoms and the presence of side effects. The study was approved by the appropriate local ethics committee.

Results

Demographics: All nine patients were female (mean age 59 years, range: 26–91 years). Five patients were referred with a postparotidectomy fistula and four with recurrent parotitis, of which two were idiopathic, one secondary to radioiodine and the other secondary to intraglandular sialolithiasis. The cases of idiopathic recurrent parotitis were diagnosed after thorough assessments including ultrasound, CT sialography, MRI and haematological investigations, with no underlying cause identified. All injections were performed by a neurologist (NM) with extensive experience with the use of BTx for neurological disorders and sialorrhoea.

Fistula group: All patients reported a fistula in the first week following their parotidectomy. Each patient was managed with a localised injection of 50 units of onabotulinumtoxinA into the residual parotid gland on the affected side under ultrasound guidance. The injections were performed in the clinic and were tolerated well. Mean time interval between onset of post-parotidectomy fistula and BTx injection was 6.4 months (range: 1–24 months). All patients reported improvement in their symptoms within one week following the injection, four with complete resolution and one with reduced salivary flow. The average follow-up for this group was 13 months (range 5 to 21 months). The patient (*Table 1*, case 4) who reported a reduction in salivary flow, but not complete resolution, did not return for follow up and declined further treatment. The other four patients reported complete closure of their fistula within a mean 2.5 weeks (range: 1–4 weeks) and therefore did not require further injections. All patients denied any side effects. Patient data is outlined in *Table 1*.

Parotitis group: Three patients with recurrent parotitis were managed with 50 units of onabotulinumtoxinA. The dose for the fourth patient was increased to 75 units following a partial response to 50 units. To confirm the anatomy of the parotid, the first injections were performed in under ultrasound guidance. All were well tolerated, and took 1–2 minutes to complete following a 3–4 minutes ultrasound to identify the anatomy. The surface landmarks were recorded diagrammatically to allow future injections with surface landmarks, with these injections typically completed within 1 minute. All patients reported an improvement with their symptoms, with one patient reporting complete resolution and three patients reporting improved symptomatology with only mild intermittent symptoms. There was a reduction in the number of courses of antibiotics the patients required, with one patient reducing from five courses a year to zero (*Table 2*, case 9). Another patient had a reduction from five courses to one course, which was required after symptoms started

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Table 1 Clinical data and outcomes of patients with a post-parotidectomy fistula

Case/ sex	Age (years)	Time from parotidectomy to Botox injection (months)	Mean dose per injection (units)	Number of treatments	Outcome from Botox injection	Time from injection to healed fistula	Follow up (months)
1/F	70	1 month	50	1	Fistula completely healed	Less than 2 weeks	8
2/F	54	3 months	50	1	Fistula completely healed	Less than 1 week	17
3/F	77	3 months	50	1	Fistula completely healed	Less than 3 weeks	15
4/F	42	24 months	50	1	Marked reduction in salivary flow	N/A	21
5/F	26	1 month	50	1	Fistula completely healed	Less than 4 weeks	5

Table 2 Clinical data and outcomes of patients with recurrent parotitis

Case/ sex	Age (years)	Pathology	Mean dose per injection (units)	Number of treatments	Mean interval between treatments (months)	Antibiotic use before injections (course/year)	Antibiotic use after injections (course/year)	Pain before injections	Pain after injections	Symptoms
6/F	48	Radioiodine	50	2	3	2	0	Occasional or moderately severe	Rare and mild	Improved but having mild symptoms intermittently
7/F	83	Sialolithiasis	50	2	3	0	0	None	None	Completely resolved
8/F	42	Idiopathic	75	5	4	5	1	Common, bothersome or affects quality of life	None	Improved but having mild symptoms intermittently
9/F	91	Idiopathic	50	1	–	5	0	Common, bothersome or affects quality of life	Rare and mild	Improved but having mild symptoms intermittently

following an upper respiratory tract infection (*Table 2*, case 8). The third patient reported a reduction from two courses a year to zero (*Table 2*, case 6). All patients had a reduction in pain in the parotid area after BTx injections. Two patients reported mild dry eyes, with no other side effects documented. Three patients are receiving ongoing injections at 3–4 months intervals to prevent further parotitis, with no reported infections since the commencement of the injections. Patient data is outlined in *Table 2*.

Discussion

Literature for the management of recurrent parotitis and post-parotidectomy fistulas with the use of BTx is expanding. However, most studies assessing these pathologies have small sample sizes due to the rarity of the conditions. Our findings suggest that BTx may be safe and effective for the management of recurrent parotitis and post-parotidectomy fistulas as all nine patients reported symptom improvement, a finding supporting current literature.

BTx is produced by the bacterium Clostridium botulinum and irreversibly inhibits neurotransmitter release from nerve terminals, blocking neurotransmission (22). Within the salivary glands, it inhibits the release of acetylcholine in the cholinergic parasympathetic secretomotor fibres and therefore reduces the production of saliva (1). However, it does not impact on the adrenergic pathway, ensuring a

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basal flow of saliva that is sufficient to avoid xerostomia (14). BTx has an onset of action on salivary glands within one week and has an expected duration of action between 3 and 5 months (23). The reduction in saliva production is presumably the basis for the improvement in both fistulae and recurrent sialadenitis, reducing flow through the fistula enables surrounding tissues to heal and preventing the pooling of saliva within the gland reducing secondary inflammation and infection (21).

All patients in our series reported a reduction in salivary flow from their fistula and four of these patients reported cessation of output and fistula resolution between 1 and 4 weeks after the BTx injection. In patients with recurrent parotitis, BTx injections reduced the number of antibiotic courses required, including one patient who was previously prescribed five courses of antibiotics each year and who subsequently did not require any further antibiotics.

The aetiology of recurrent parotitis directs the management (18-20). Two of our patients have idiopathic recurrent parotitis, confirmed after comprehensive investigations, which is managed with conservative interventions including antibiotics, oral steroids and analgesia. However, the efficacy of these interventions is poor and most patients will require formal parotid gland excision for definitive management (18). One patient had recurrent parotitis secondary to a large intraglandular sialolith, which was not amenable to sialendoscopy (19). The last patient had recurrent parotitis secondary to radioiodine accumulation, following management for thyroid carcinoma. Papers have documented promising results for the use of sialendoscopy for idiopathic and radioiodine accumulated parotitis, however our patients opted for BTx after a discussion of the management options. There is potential for BTx to be used for a range of aetiologies of recurrent parotitis given its ability to reduce salivary output and therefore reduce the pooling of saliva.

The use of BTx for recurrent parotitis is limited by its requirement for injections at three to six monthly intervals. However, the regular use of BTx is preferable over the ongoing requirement of antibiotics, given the increased risk of antibiotic resistance. Our patients also preferred the injections, given the simplicity of the injection process. We attempted to prolong the injection intervals, however when a patient reported an onset of symptoms we resumed injections at the previous interval times for that patient. One patient with recurrent parotitis required only one set of injections of BTx, with no further symptoms, an unusual occurrence that has been previously described in a case study (17).

Ultrasound guidance for injections is particularly useful when the parotid anatomy is distorted, such as post-parotidectomy and when there is substantial scarring or swelling following recurrent infections. Ultrasound may facilitate the spread of toxin through the whole gland and limit spread to surrounding structures (12). All treatments were performed in the clinic and were well tolerated. No significant side effects have been reported in the literature. In our series, two patients complained of mild transient dry eyes following injection of the toxin into the parotid, a previously unreported side effect in studies assessing BTx in parotid gland pathology. Despite a reduction in salivary flow from the injected parotid gland, no patients reported a dry mouth, suggesting that the basal flow from the parotid gland in conjunction with other salivary glands, including the contralateral parotid, provides adequate saliva to prevent xerostomia. While patients in our series with recurrent parotitis had conditions affecting unilateral parotid glands, there is potentially scope for bilateral injections of the parotid simultaneously given basal salivary flow may prevent xerostomia.

Current literature provides guidance but no clear consensus regarding the dose of BTx that should be injected for the management of either post-parotidectomy fistulas or recurrent parotitis. Our treatment protocol stipulated that we commenced all patients on an injection of 50 units into the parotid gland or residual salivary tissue, which was adequate for a clinical response in most patients. However, case 8 (*Table 2*) required a dose increase to 75 units due to an incomplete response to 50 units.

BTx has been recommended as a treatment option only when conservative management fails (4). In our series, management initiated before referral to our team varied, with some patients having a period of conservative management and others immediately referred. Laskawi and colleagues argue that BTx should be used in the early management of post-parotidectomy fistulas given the immediate reduction in salivary flow (3). We recommend a 4-week trial of conservative management, including pressure bandages, suturing, glycopyrrolate and diet restrictions, prior to BTx treatment. In our experience, conservative interventions seldom work. Adjuvant radiotherapy to the surgical site for patients with known malignancy typically aids fistula healing though the reduction of salivary outflow. However, patients can have associated facial and neck swelling which can impact on the design and use of the immobilisation mask and therefore alter the radiotherapy

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fields. In these cases, BTx may reduce the swelling to enable better design and use of the mask.

Our study is limited by our small sample size, however given the rarity of the conditions this is expected and is demonstrated in other small published case series. Furthermore, patients completing the questionnaire about pre-BTx symptoms after the intervention is limited by their recall, however we correlated questionnaire answers with pre- and post-injection clinical notes.

Conclusions

The therapeutic scope of BTx has expanded to include recurrent parotitis and post-parotidectomy fistulas. The findings of our case series of nine patients suggest that BTx could be effective and safe in the management of post-parotidectomy fistulas and recurrent parotitis secondary to radioiodine accumulation, intraglandular sialolithisis or idiopathic, which supports the literature. We advocate for the early use of BTx in the treatment of these pathologies.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/ajo.2018.01.05). JR serves as an unpaid editorial board member of *Australian Journal of Otolaryngology*. FR serves as an unpaid editorial board member of *Australian Journal of Otolaryngology*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the appropriate local ethics committee. All patients gave informed consent, including the limited evidence for its use, theoretical rationale and potential adverse effects.

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doi: 10.21037/ajo.2018.01.05
Cite this article as: O'Neil LM, Palme CE, Riffat F, Mahant N. Local experience using botulinum toxin for the management of post-parotidectomy fistulas and recurrent parotitis. Aust J Otolaryngol 2018;1:3.

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