

REVIEW

Botulinum toxin A is an effective therapeutic tool for the management of parotid sialoceles and fistula: A systematic review

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Abstract

Objectives: In the management of parotid sialoceles and fistula, various conservative and surgical methods have been described. Some studies have described the use of Botulinum toxin A (Botox A) for the management of parotid sialoceles and fistula. This is a less invasive and potentially equally effective option. We therefore conducted a systematic review on the current body of literature relating to this specific use of Botox A.

Methods: A search strategy was conducted in July 2019 using the following electronic databases: Cochrane Database of Systematic Reviews, EMBASE, Google Scholar, PubMed, Scopus, and Web of Science. A search of all articles from inception until 31 August 2019 was performed.

Results: Literature searches of electronic databases identified 67 articles eligible for review, of which 15 fulfilled all criteria. These studies were small and in total only 47 patients were included. The majority of sialoceles and fistulas presented as a complication of surgery (77%) with the remaining cases occurring as a result of trauma. The typical age at presentation was between 32 and 88 years of age (mean age of 52 years). All patients were initially treated with and failed other conservative measures. Botox A injection was considered as a final conservative treatment option. The toxin was administered percutaneously in all cases of parotid sialoceles and fistula. Dosage of Botox ranged from 10 to 200 units with majority of patients (58%) requiring only one injection. The overall success rate for patients treated with Botox A injections ranged between 70 and 100% for parotid sialoceles and fistulas.

Conclusion: Botox A injections are successful in the treatment of parotid sialoceles and fistulas and should be considered before the use of invasive conventional options. Further studies with larger numbers are needed to ratify this recommendation. Success rate for patients, treated with Botox A injection was between 70 and 100% for parotid sialoceles and fistula. Patients who failed initial treatment with Botox A were re-administered with Botox A and eventually resolved.

KEYWORDS

Botox A, botulinum toxin A, parotid fistula, parotid sialoceles

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1 | INTRODUCTION

Parotid sialoceles are defined as an accumulation of saliva in the subcutaneous tissue around the gland or duct.¹⁻³ This occurs because of blunt or penetrating trauma to the parotid gland or duct, or as a complication of surgery.³

The clinical presentation includes that of a painless swelling around the parotid gland or duct and may be complicated by fistula formation and infection.³ Though parotid sialoceles and fistulas are two different clinical entities, a parotid sialocele may progress to a parotid fistula. Hence, early appropriate treatment of a sialocele is recommended. The incidence of sialocele/fistula development has been reported to be between 2 and 6.4% in patients undergoing partial superficial parotidectomy.³

At present, definitive evidence-based treatment guidelines for sialocele and fistula management do not exist. In the management of parotid sialocele/fistula, various conservative and surgical methods have been described. Botox A is a neurotoxin which inhibits presynaptic acetylcholine release and hence saliva production from parotid glandular tissue.³ Its uses for facial cosmesis are widely documented.⁴⁻⁸ It has minimal side effects when injected locally. Few studies have described the use of Botox for the management of parotid sialocele. There is therefore a need to further explore the use, benefit, method of administration and optimal therapeutic dose of Botox A in the management of parotid sialoceles.⁸ We therefore conducted a thorough literature search and formulated this review on the current body of information relating to this topic.

The aim of this systematic review was to synthesize the evidence from primary research studies and formulate recommendations on the use of Botox A injections in adult patients with parotid sialocele and fistula.

2 | MATERIALS AND METHODS

2.1 | Search strategy

A search strategy was conducted in August 2019 using the following electronic databases: Cochrane Database of Systematic Reviews, EMBASE, Google Scholar, PubMed, Scopus and Web of Science. A search of all articles from inception until 31 August 2019 was performed. Using a keyword search strategy, studies were identified and verified independently by two authors (S.Ma., S.Mu.). The following terms were searched: Botox or Botox A or Botulinum toxin A and (parotid sialocele or parotid fistula). Citations of all papers retrieved were also analyzed for additional relevant resources. The search was restricted to publications in the medical literature.

2.2 | Study selection

Studies included in the review met the following criteria: (a) English language, (b) availability of data, (c) patients treated medically with Botox A, and (d) clinical publications, were used as inclusion criteria. Data points extracted from each study included number of patients, patient demographics, anatomical site of parotid affected, indications

for therapy, dosage, method of Botox administration, frequency of therapy, adjunct use of other conservative measures, complications, outcomes, and average follow-up duration.

2.3 | Review study definition of botulinum use for the treatment of parotid sialocele

In this study, the use of Botox A for the medical treatment of parotid sialocele or fistula, alone or in combination with surgery or other treatment adjuncts was deemed adequate for study inclusion. Response to Botox A was defined as any clinical or radiological outcome detected after administration of the drug.

2.4 | Data extraction and methodical evaluation

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were applied to guide the electronic search. Eligible articles were screened by each reviewer. The selected studies were ranked using the ROBINS-1 tool for assessing risk of bias in nonrandomized studies of interventions. Each reviewer then compiled a descriptive narrative of each study (Table 1).

The following PICOS (Participants, Interventions, Comparisons, Outcomes, and Study design) criteria were utilized. The patient population included all patients with parotid sialocele or fistula who were treated conservatively with Botox A. The comparison was between various administration techniques and dosages of Botox A.

The outcomes included the effectiveness of Botox A on parotid sialocele or fistula, specifically the persistence or resolution of the sialocele or fistula following administration. Due to the sparsity of literature related to our topic, the setting included all studies relevant to the use of Botox A for parotid sialocele and parotid fistula, including all case reports and case series.

The points of interest in each study were tabulated. These included number of patients, patient demographics, anatomical site of parotid affected, indications for therapy, dosage, method of Botox administration, frequency of therapy, adjunct use of other conservative measures, complications, outcomes and average follow-up duration and author conclusions or comments. Risk of bias was addressed as assessments were completed by more than one person, and they were completed independently of each other.

Conflicting entries, disagreements, and differences were resolved by consensus among the reviewers.

3 | RESULTS

3.1 | Search

The literature search began by broadly searching for any references of Botox A, botulinum toxin A, parotid sialocele, parotid fistula, ultimately coning down to identify relevant citations. Articles not in English were

TABLE 1 Risk of bias table

Author, date, country	Bias due to deviations from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results
Lim, Choi (2008), South Korea	Low	Low	Low	Low
Marchese-Ragona, Marioni, Restivo, Staffieri (2006), Italy	Low	Low	Low	Low
Arnaud, Batifol, Goudot, Yachouh (2006), France	Low	Low	Low	Low
Laskawi, Winterhoff, Köhler, Kottwitz, Matthias (2013), Germany	Low	Low	Low	Low
Hill, Mortimer, Hitchcock (2007), New Zealand	Low	Low	Low	Low
Send, Bertlich, Eichhorn, Bootz, Jakob (2019), Germany	Low	Low	Low	Low
Ferron, Cernea, Almeida, Cesar (2017), Brazil	Low	Serious	Serious	Moderate
Ahuja, Natarajan, Galinde, Asnani (2017), India	Low	Low	Low	Low
Çalış, Mert; Öz, Zeynep; Uzun, Hakan; Özgen, Burçe; Çetin, Alp; Aksu, Emre (2017), Turkey	Low	Moderate	Serious	Moderate
Melville, Stackowicz, Jundt, Shum (2016), United States	Low	Moderate	Moderate	Serious
Chow, Kwok (2003), Hong Kong	Moderate	Moderate	Low	Low
Krishan, Clark, Donnelly (2009), United States	Moderate	Low	Moderate	Moderate
Hatzis, Finn (2007), United States	Moderate	Low	Low	Moderate
Guntinas-Lichius, Sittel (2001), Germany	Moderate	Low	Moderate	Low
Gok, Michl, Williams, Howlett (2015), United States	Moderate	Low	Low	Moderate

immediately excluded. Once relevant citations had been identified and reviewed, articles in which relevant information could not be extracted or was not reported within the article were also excluded.

Literature searches of electronic databases identified 67 articles suitable for review. The breakdown is as follows: Cochrane Database of Systematic Reviews (0), EMBASE (0), Google Scholar (32), PubMed (28), Scopus (7), and Web of Science (0). After review, 40 articles were excluded due to insufficient detail, duplicate articles, articles not in English, use of other types of Botulinum toxin and insufficient data for meaningful analysis. The remaining 27 articles were then fully reviewed. Sialoceles involving salivary glands other than the parotid, irrelevant articles or where the full text was not available was then further excluded. Fifteen articles were finally selected for inclusion in the systematic review, which included a cumulative total of 47 patients across all studies (Table 2).

3.2 | Study design of included studies

All studies were retrospective and consisted of mostly case reports. Follow-up was variable and ranged from 10 days to 21 months. A breakdown of analyzed studies can be seen in Table 2.

3.3 | Study population of included studies

All the studies had human participants. Majority of sialoceles and fistulas presented as a complication of surgery (77%) with the remaining cases occurring as a result of trauma. Surgery performed included parotidectomy

for tumor excision and Mohs micrographic surgery. Surgery was performed for diagnosis of squamous cell carcinoma in most cases.

3.4 | Age of patients

In our review of studies, which indicated the gender of patients, males were more commonly affected than females. The typical age at presentation was between 32 and 88 years of age (mean age of presentation: 52 years).

3.5 | Overall and study sample size

The total number of subjects across all studies was 47 patients. The largest study had 16 participants while the smallest included manuscript had 1 subject.^{9,10,12,17-20,23} The mean sample size of all included studies was 3.5 (SD 40.8).

3.6 | Male to female ratio

There were more males than females with a male to female ratio of 2.5:1.

3.7 | Region of study origin

Among the 15 studies, three were conducted in the United States^{8,17} and Germany, respectively, and one in Turkey,¹⁸ United Kingdom,

TABLE 2 Studies that fulfilled the inclusion criteria

Author, date, country	Study design	n	Intervention	Comparator	Results	Side effects
Lim, Choi (2008), South Korea ⁹	Case report	1	Indications: salivary fistula-iatrogenic postparotidectomy for tumor Method of injection: transcutaneous Dose: 10 units Route: parotid gland, 5 iu and 5 iu 1 cm apart using tuberculin syringe Frequency: once	Nil	Nil complications reported and condition resolved. Follow-up in 6 months This report suggests that the injection of botulinum toxin type A is a highly effective and relatively safe primary method of treatment for an acute postparotidectomy salivary fistula, and not merely an alternative to more conservative therapy	
Marchese-Ragona, Marioni, Restivo, Staffieri (2006), Italy ¹⁰	Case series	3	Indications: salivary fistula-iatrogenic postparotidectomy for tumor Method of injection: percutaneous Dose: 10 units/15 units/20 units Route: parotid gland, 10 iu—2 injections at different sites of 5 iu each 15 iu—3 injections at different sites of 5 iu each 20 iu—3 injections at different sites to a total of 20 units Frequency: once	Pressure dressing	Nil complications reported and condition resolved. Follow-up in 21, 18, and 14 months, respectively In the considered cases, the localized injection of botulinum toxin into the parotid gland resulted to an effective and long-lasting treatment of postparotidectomy fistula	Nil observed
Arnaud, Batifol, Goudot, Yachouh (2006), France ¹¹	Case report	1	Indications: sialocele post-trauma Method of injection: transcutaneous Dose: 100 units Route: parotid duct, single injection Frequency: 3, second injection 3 months after injury, third 9 months after injury	Nil	Nil complications reported and condition resolved. In our opinion, an excellent alternative therapy for sialoceles and fistulas, because of its efficiency, few side effects, and minimal drawbacks for the patient. Injections of botulinum toxin type A can be used in first intention without associated mechanical or pharmacological treatment	
Laskawi, Winterhoff, Köhler, Kottwitz, Matthias (2013), Germany ¹²	Case series	12	Indications: salivary fistula-iatrogenic postparotidectomy for tumor and sialocele Method of injection: percutaneous (2 of the 12 patients had initial percutaneous then later	Injection under ultrasound guidance into residual parotid glandular tissue. Surgical fistula excision and post-op radiation (30 Gy). Early revision surgery-microsurgical extirpation.	Nil complications reported and condition resolved in 10 of the 12 patients. A persistent fistula reported in 1 patient and in another patient the condition persisted, eventually resolved after radiation	

(Continues)

TABLE 2 (Continued)

Author, date, country	Study design	n	Intervention	Comparator	Results	Side effects
			intraoperative botox application to fistula Dose: total dose between 10 and 40 units Route: parotid gland, single injection during each application Frequency: 1-2	Radiotherapy	completed. Follow-up differed in all patients ranging from 10 days to 6 months to 14 days In summary, botulinum toxin injections into the parotid tissue remaining after surgery appear to be an effective treatment for salivary fistulas following parotidectomy	
Hill, Mortimer, Hitchcock (2007), New Zealand ¹³	Case report	1	Indications: parotid fistula-iatrogenic, postexcision carcinoma cheek Method of injection: percutaneous Dose: 225 units Route: parotid duct, single injection Frequency: once	Ultrasound guidance	Nil complications reported and condition resolved. Follow-up in 6 months	
Send, Bertlich, Eichhorn, Bootz, Jakob (2019), Germany ¹⁴	Case series	16	Sixteen patients with salivary fistula received 27 injections of botulinum toxin. Nine patients required one injection for the fistula to heal, five patients needed two injections, and one patient needed three and four injections, respectively. No patient underwent additional surgery or radiotherapy		In most cases of salivary fistula, injections of botulinum toxin are a valid treatment. If the initial injection is not successful, injections may be repeated once. Otherwise, revision surgery should be considered. In general, treatment with botulinum toxin should be commenced in an earlier stage and with higher dosages	No adverse effects reported
Ferron, Cernea, Almeida, Cesar (2017), Brazil ¹⁵	Case report	1	Indications: iatrogenic Dose: 32 units in two applications, first application of 16 u with 8 mm needle presented no improvement, second application of 16 u with 40 mm needle was performed after 7 days and reached the salivary gland effectively Route: parotid duct	The use of long needles is recommended when ultrasound is not available to guide the application		
Ahuja, Natarajan, Galinde, Asnani (2017), India ⁷	Case report	1	Indications: excision of myxoma Method of injection: percutaneous Dosage: 50 units, 2 doses of 20 u administered each 1 week apart Route: parotid duct		Nil complications reported and condition resolved. Follow-up done every alternate day and after 2 weeks' salivary leakage and swelling completely resolved Percutaneous injection of botulinum toxin type A,	Not evident

(Continues)

TABLE 2 (Continued)

Author, date, country	Study design	n	Intervention	Comparator	Results	Side effects
					is an effective conservative treatment approach for effective management of parotid sialoceles, that should be considered before performing an invasive surgical procedure	
Çalış, Mert; Öz, Zeynep (2017), Turkey ¹⁶	Case series	3	Indications: trauma, iatrogenic, Mohs treatment Dosage: concurrently, 100 units of botulinum toxin A was injected at standardized eight points to the parotid gland Route: parotid duct			
Melville, Stackowic, Jundt, Shum (2016), United States ¹⁷	Case series	3	Indications: iatrogenic, Mohs treatment		With the Botox, the nonhealing wound resolved and the drain was removed at least 2 weeks before the initiation of adjunctive radiotherapy, thus minimizing delay in adjuvant treatment	
Chow TL, Wok K (2003), Hong Kong ¹⁸	Case report	1	Indications: iatrogenic Superficial parotidectomy			
Krishan, Clark, Donnelly (2009), United States ¹⁹	Case report	1	Indications: iatrogenic, parotid lesions Intraparotid injections of Botox A		With the Botox A, the lesion resolved after 2 weeks of administration	
Hatzis, Finn (2007), United States ²⁰	Case report	1	Indications: iatrogenic, mohs surgery, parotid lesions Intraparotid injections of Botox A	Pressure dressings, glycopyrrolate	With the Botox A, the lesion resolved after 2 weeks of administration	
Guntinas-Lichius, Sittel (2001), Germany ²¹	Case report	1	Indications: iatrogenic Superficial parotidectomy Intraparotid injections of Botox A, including the deep lobe		With the Botox A, the lesion resolved, and was monitored for 11 months postintervention	
Gok, Michl, Williams, Howlett (2015), United Kingdom ²²	Case report	1	Indication: late complication, gunshot injury to the face	Ultrasound guided Injections of Botox A	With the Botox A, the lesion resolved	

Hong Kong, India, Brazil, Italy, South Korea, France, and New Zealand, respectively.

3.8 | Diagnosis and location

Unilateral swelling over the parotid area containing clear fluid in the case of sialoceles or clear fluid draining from the skin defect in salivary fistula, were reported throughout most studies.

The most common diagnostic test was a salivary amylase level, which was elevated. This is obtained either via aspiration of the sialoceles, or by collection of clear fluid draining from the fistula. CT scan and ultrasound was also helpful in some cases to confirm the diagnosis.

The most common anatomical site involved was parotid glandular tissue, which was the more commonly injured than the parotid duct. Parotid fistulas occurred more frequently than parotid sialoceles.

3.9 | Treatment approach and technique

All patients were initially treated conservatively and failed conservative management including repeated aspirations, compression dressings, and anticholinergic medication. Botox A injection was considered as a final conservative treatment option. Botox A was administered percutaneously in all cases of parotid sialoceles and fistula.

Timing to administration varied across the studies and the number of injections depended on response to treatment. Some authors administered the Botox as a single injection into the affected area whereas others opted to mark individual points on the affected area (2-14 points) and administer the Botox in divided doses among these injection points.

Administration of Botox under ultrasound guidance was done in 41% of cases. All cases of sialoceles were treated with aspiration immediately before the injection of Botox, and one study used concomitant drain insertion and Botox injection for sialoceles treatment. Two studies used pressure dressings in addition to Botox A injection until follow up, and one study used pressure dressings and anticholinergic medication in conjunction with Botox treatment for iatrogenic parotid fistula.

Dosage of Botox ranged from 10 to 200 units with 58% of patients requiring only one dose.

3.10 | Success rates

The overall success rate for patients treated with single dose Botox A injection was between 70 and 100% for parotid sialoceles and fistula. Patients who failed initial treatment with Botox A were given repeated doses and resolved. In cases of iatrogenic parotid fistula post-tumor excision, radiotherapy was administered in addition to the Botox injection, which aided in symptom resolution.

Glycopyrrolate and compression dressings may also be used simultaneously as conservative treatment options with Botox A injections. Duration of response to therapy may be affected by the size of the fistula, patient's nutritional status, comorbidities, and amount of residual glandular tissue present. Follow-up periods with complete resolution ranged from 10 days to 21 months depending on whether the patient required multiple injections and concomitant post-op radiotherapy.

4 | DISCUSSION

Management of patients with parotid sialoceles is a contentious issue due to the variety of treatment options and paucity of studies of an adequate size. In reviewing the literature, the following trends are evident.

The etiology of parotid sialoceles and fistula is most commonly iatrogenic, with trauma being the second most common cause of injury. Parotidectomy for tumor excision is the most common procedure associated with sialoceles and fistula formation.

Clinical presentation includes that of a painless swelling around the parotid gland or duct and may be complicated by fistula formation

and infection.³ Patients may also present with aesthetic concerns as the swelling may continue to enlarge if not managed.

Radiologic investigations may aid in diagnosis, assist in evaluation of extent of the site affected and thereby assist in management strategies for sialoceles. Fistulography refers to a technique in which radiopaque contrast is injected into the fistula, often under fluoroscopic guidance to visualize the extent of the tract.^{3,4} Sialography involves cannulation of the opening of the duct and injection of water-soluble contrast and provides useful information about the extent of ductal injury.^{3,4} Ultrasonography may demonstrate a cystic lesion which contains complex fluid.⁴ CT fistulography or CT sialography may also demonstrate the extent of anatomical disruption and will show a simple or multiloculated cystic mass with smooth borders, and of lower density than surrounding structures.⁴ MRI is usually unnecessary but may indicate a cystic mass with low signal intensity on T1-weighted imaging and high signal intensity on T2 weighted imaging.⁴

Fine needle aspiration and laboratory analysis of fluid demonstrate a high salivary amylase level of >10 000 units/L, thus confirming the diagnosis of sialoceles in cases of uncertainty.⁴

There is no consensus regarding conservative vs surgical management for parotid sialoceles. Surgical management includes primary repair or reconstruction of the duct using graft material, or the use of buccal mucosal flaps in the case of distal ductal injuries.^{3,5} Control of fistula can be achieved by placement of a polyethylene catheter, T-tube or catheter drain into the proximal duct to allow drainage of saliva into the oral cavity.³

Ligation of the parotid duct may result in glandular atrophy, and diminished saliva production as a result.³ Parasympathetic denervation via sectioning of the auriculotemporal nerve may have a similar result.⁵

Superficial total parotidectomy may also be performed.⁵ Surgical procedures are, however, invasive and may not always have successful results.^{5,6}

Conservative management options include repeated aspirations and compression dressings, antisialagogue use and radiotherapy at a dose of 6 to 20 Gy.⁵ Botox use for persistent parotid sialoceles is recognized as a viable option to surgical management.⁷ There is however, limited documented evidence on the use of Botox in sialoceles involving the parotid duct.^{5,6}

Botox A is a neurotoxin, which inhibits presynaptic acetylcholine release.³ It acts locally, with minimal side effects and its use for facial cosmetics, sialorrhoea and sialoceles is widely documented.⁸ The method of administration and optimal therapeutic dose of Botox, however, is still contentious.⁸ There is also no clear evidence on the use of percutaneous Botox A injection for sialoceles resulting from complete transection of the parotid duct.

4.1 | Strengths and limitations of review

One of the main strengths of this review is the breadth of the search strategy. There has been one previous systematic review that examined the efficacy of Botox A in postsurgical parotid fistula. This study

was published in April 2019 and included nine studies of botulinum toxin used in the treatment of a total of 25 patients.

Our review has been able to include a number of studies published since then. Our review includes 15 studies of a total of 47 patients.

5 | CONCLUSION

In this review article, the majority of sialoceles and fistulas presented as a complication of surgery (77%) with the remaining cases occurring as a result of trauma. Surgery performed included parotidectomy for tumor excision and Mohs micrographic surgery. Surgery was performed for diagnosis of squamous cell carcinoma in most cases.

The typical age at presentation was between 32 and 88 years of age (mean age of presentation 52 years).

The most common diagnostic test is the salivary amylase level, which is elevated. This is obtained either via aspiration of the sialocele, or by collection of clear fluid draining from the fistula. CT scan and ultrasound was also helpful in some cases to confirm the diagnosis.

Botox A injection was considered as a final conservative treatment option. All patients were initially treated conservatively and failed to respond to other conservative management strategies. The toxin was administered percutaneously in all cases of parotid sialocele and fistula.

The success rate for patients in this review, on initial treatment with Botox A injection was between 70 and 100% for parotid sialocele and fistula. Patients who did not respond after the first treatment were re-administered with Botox A and eventually resolved.

This systematic review has critically appraised the available evidence on the effectiveness of Botox A injections as an intervention to manage parotid sialoceles and fistulas. The review process has highlighted the paucity of existing evidence to support botulinum toxin A treatments for salivary sialocele and fistula, the lack of randomized controlled trials in this area, and highlights the need for further studies. Due to the small number of subjects and the variable quality of the study designs included in this review, the results must be interpreted with caution.

CONFLICT OF INTEREST

The authors declare no potential conflict of interests.

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