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Management of first bite syndrome: systematic review of recent evidence

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Review Article

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Abstract

Objective. First bite syndrome refers to pain in the parotid region during the first bite when eating that improves with subsequent bites. There is a paucity of evidence in the literature to justify recommending optimal management therefore this study aimed to review the latest evidence for its management.

Methods. A literature search across four databases was conducted using a Population, Intervention, Comparison, Outcome-generated search strategy between 2012 and 2022. Screening was done by two reviewers according to pre-determined inclusion and exclusion criteria, demonstrated in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart.

Results. Eleven articles were included. Six articles used repeated botulinum toxin injection, which in all the studies resulted in complete symptoms resolution. Four articles found a watch-and-wait technique to be effective. There were conflicting results on the efficacy of medical treatments such as opioids or anticonvulsants.

Conclusion. Studies have shown that first bite syndrome symptoms eventually resolve with conservative management, but repeated botulinum toxin appeared efficacious for quicker symptom resolution. Further higher-quality studies should be conducted to identify the optimal management.

Introduction

First bite syndrome was first defined by Netterville *et al.* as severe sharp or cramping pain in the parotid region that occurs with the first bite of mastication and improves with subsequent bites.[1] First bite syndrome most commonly occurs as a post-operative complication. The incidence of first bite syndrome as a complication after parotid or parapharyngeal surgery is rare, but has been found to range between 9.6 and 18 per cent for deep lobe parotid surgical procedures.[2,3]

Far less commonly, first bite syndrome has been observed following other surgical procedures, including carotid endarterectomy, bimaxillary osteotomy and bilateral temporomandibular joint replacement.[4–6] It has also been described in cases of parotid or submandibular malignancies, in the absence of any surgical intervention.[7,8] In these instances, surgical resection of the tumour may bring relief to patients suffering from first bite syndrome.

Certain risk factors, such as female sex, younger age and existing symptoms before surgery, have been found to be associated with the development of first bite syndrome.[2,9] In one of the largest cohort studies undertaken, following post-surgical patients who developed first bite syndrome, Linkov *et al.* found that tumours arising in the parapharyngeal space and parotid region had a higher risk of first bite syndrome, whereas it was not seen in tumours arising from the infratemporal fossa.[2] These researchers also found that the majority of parotid first bite syndrome cases arose from deep lobe pathology and/or surgery,[2] although another study did not identify this association between parotid pathology location and incidence of first bite syndrome.[9]

Additionally, Linkov *et al.* found that there were higher incidences of first bite syndrome when the sympathetic chain was sacrificed, when dissection involved the parapharyngeal space and when resection involved the whole parotid gland.[2] These independent predictors of first bite syndrome may be explained by the most widely accepted aetiology of first bite syndrome. It is proposed that during surgical dissection or exploration, loss of sympathetic innervation to the parotid gland leads to denervation of sympathetic receptors located on the parotid myoepithelial cells. These cells also possess parasympathetic receptors, which become hypersensitive to unopposed parasympathetic simulation. This leads to an intense parasympathetic contractile response at the first bite, causing pain.[1]

Treatment for first bite syndrome is varied, ranging from conservative observation to medication and procedural interventions. The last published literature review based on first bite

Table 1. Use of PICO tool to generate the literature search strategy

Criteria	Study
Population	Any patient with first bite syndrome following surgery
Intervention	Active treatment
Comparison	Conservative management
Outcome	Symptomatic improvement

syndrome was done by Laccourreye *et al.* in 2013,[10] and multiple treatment options were explored. Non-steroidal anti-inflammatory drugs, acupuncture or common analgesia such as paracetamol or codeine were not found to be effective.[11–14] There were mixed results with carbamazepine, gabapentin or pregabalin, with some studies showing partial improvement[13,15] and others demonstrating no effect.[16,17] Neoadjuvant radiotherapy was found to reduce the incidence of first bite syndrome post-neck lymph node dissection, although this carries a significant side-effect profile.[12,13,18] Two studies utilised botulinum toxin injections, which resulted in complete resolution of first bite syndrome symptoms.[14,19] Multiple studies also reported complete symptom resolution without any intervention after a period of several months to one year of observation.[13,16,18,20]

First bite syndrome significantly impairs quality of life because pain associated with eating leads to diet change and meal avoidance.[2] The last literature review exploring management options for first bite syndrome was in 2013, which found botulinum toxin injections to be the most effective first-line treatment option, although as it was a relatively new method the injection protocol and long-term efficacy were not clearly defined.[10] Since then, there have been many related published articles looking at management options for first bite syndrome, including cohort studies, case series and case reports. This study aimed to review the latest literature since then, analysing the treatment options available in managing first bite syndrome and their efficacy, with particular attention on new evidence for botulinum toxin injections.

Methods

Literature search strategy

This review was carried out based on guidelines for robust systematic reviews recommended by Tawfik *et al.*[21] A preliminary search was performed with the search terms 'first bite syndrome' and 'treatment' in PubMed. This was to ensure there was sufficient evidence in the current literature for the authors to conduct this systematic review, and to ensure there were no similar studies published recently. The authors identified a systematic review undertaken by Laccourreye *et al.*[10] in 2013, therefore it was decided to limit our search to the 10-year period between January 2012 and January 2022 to provide an up-to-date account since then.

The Population, Intervention, Comparison, Outcome tool was utilised to develop our literature search strategy, as shown in Table 1.

The search strategy '(first bite syndrome) AND (treatment OR management OR therapy)' was used across four databases: PubMed and/or Medline, the Cochrane Database of Systematic Reviews, ProQuest and ScienceDirect. Articles were then screened through following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart.

Inclusion and exclusion criteria

Articles concerning any form of treatment for first bite syndrome were included in our analysis. Papers focused on the aetiology or pathogenesis of first bite syndrome were excluded, and studies that looked at other surgical complications, such as Frey's syndrome, were also excluded. Articles that reviewed treatment options prior to January 2012 were excluded. Abstracts, conference titles, books, letters to editors and articles that were not in English were excluded. All articles were screened by two independent reviewers and the results compared.

Data extraction

The data extraction process for the included articles was done by two authors (W.W.A. and E.T.G.). The extracted data included year, country, study design, number of patients treated, demographic (including age and sex), treatment used, patient outcome (as defined by individual studies) and follow-up period. The extracted data were then tabulated to facilitate data interpretation and analysis.

Quality assessment of studies

The quality of studies included was also assessed using the appropriate Study Quality Assessment Tool templates by the National Heart, Lung, and Blood Institute based on the type of study.[22] This process was done independently by two reviewers (W.W.A. and E.T.G.), and an overall quality rating was given to each study once a consensus was achieved.

Results

Literature search result

The search yield and screening process is shown in Figure 1.

Thirty-six articles were included for full-text review after initial abstract screening, alongside one other article identified through related articles. The 37 full-text articles were reviewed by two authors (W.W.A. and E.T.G.). Sixteen articles were deemed irrelevant, five comprised reviews of current treatments, three were not in English, and we were unable to obtain full text for two articles. This resulted in 11 articles that were ultimately included in this review.

Study characteristics and patient demographics

The extracted data from the 11 included articles regarding study characteristics and patient demographics are displayed in Table 2. There was one cohort study,[2] five case series[9,23–25] and five case reports.[26–30] A total of 96 patients (64 females, 32 males) were treated for first bite syndrome, although in one study 13 patients were lost to follow up[31] so the authors could only obtain treatment outcomes for 83 patients. The mean age across all 96 patients was 51.37 years (20–89 years). During the data-collection process, the authors noted that most patients experienced first bite syndrome as a post-operative complication, which included superficial or deep parotidectomies, neck dissections, parapharyngeal surgery, temporomandibular joint surgery or transoral robotic surgery. However, there were three patients in Handa *et al.*'s case series who had idiopathic first bite syndrome.[31]

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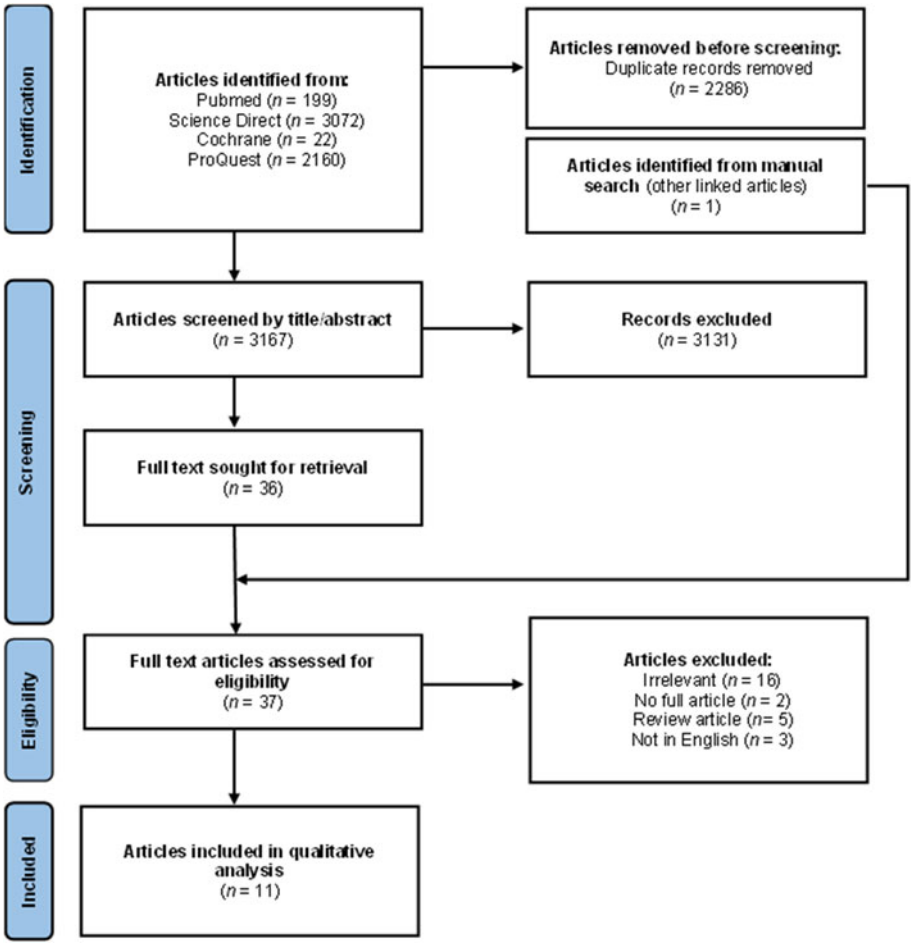

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart showing the article selection process for this review.

Table 2. Data extracted from the 11 articles included in the review

Authors	Year	Country	Study design	Number treated	Age (mean (range); years)	Gender
Lammek *et al.*[9]	2021	Poland	Case series	7	42.7 (29–54)	7 female
Sims and Suen[25]	2013	USA	Case series	3	48.3 (34–67)	2 female, 1 male
Linkov *et al.*[2]	2012	USA	Cohort study	45	–	31 female, 14 male
Handa *et al.*[31]	2022	USA	Case series	24–13 lost to follow up	50.8 (20–89)	18 female, 6 male
Kesayan *et al.*[26]	2020	USA	Case report	1	70	1 male
Ghosh and Mirza[23]	2015	USA	Case series	5	53.6 (29–77)	3 female, 2 male
Topf *et al.*[24]	2018	USA	Case series	6	58.8 (43–67)	6 male
Fiorini *et al.*[27]	2015	Italy	Case report	2	50	1 female, 1 male
Amin *et al.*[29]	2014	UK	Case report	1	70	1 female
Dubyk *et al.*[28]	2022	USA	Case report	1	43	1 male
Gunter *et al.*[30]	2021	USA	Case report	1	53	1 female

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Table 3. Treatment options and corresponding treatment outcomes for the 11 articles included in the review

Author	Number treated	Treatment (*n*)	Outcome	Follow-up period (months)
Lammek *et al.*[9]	7	Conservative treatment (7)	Complete resolution of symptoms	12
Sims and Suen[25]	3	75 U botox (3), repeated injections required in four-month intervals	Complete resolution of symptoms up until follow-up period	38
Linkov *et al.*[2]	45	Analgesia (14), neuropathic pain medication (10), botox (1), acupuncture (1), conservative (30)	31 out of 45 symptoms improved, 14 out of 45 persistent symptoms	40
Handa *et al.*[31]	24 – 13 lost to follow up	Botox 80–100 U every three months (1)	Complete resolution of symptoms	–
		Conservative (2)	Complete resolution of symptoms	
		Gabapentin and/or Botox (8)	No response or partial treatment	
Kesayan *et al.*[26]	1	Medical: pregabalin, carbamazepine, gabapentin, amitriptyline	Failed to improve symptoms	–
		Trigeminal nerve block and Radiofrequency ablation	Symptoms improved but returned after five weeks	
		Botox, 50 U followed by 65 U	Symptoms improved but returned after five weeks, after second injection symptoms resolution	
Ghosh and Mirza[23]	5	Botox (5), 10–40 U (number of repeated injections between 0 and 4)	Repeated every four months until complete resolution	36
Topf *et al.*[24]	6	Pregabalin (1)	Complete resolution of symptoms	3–4
		Conservative (3)	Complete resolution of symptoms	
		Opioids (1)	Complete resolution of symptoms	
		Gabapentin, then botox (1)	Improvement of symptoms	
Fiorini *et al.*[27]	2	Acupuncture (2)	Complete resolution of symptoms	1.5
Amin *et al.*[29]	1	Laser tympanic plexus ablation (1)	Complete resolution of symptoms	2
Dubyk *et al.*[28]	1	Botox (1), 3 injections of 50 U	Complete resolution of symptoms	Ongoing
Gunter *et al.*[30]	1	Conservative (1)	Complete resolution of symptoms	12

Treatment methods, outcomes and follow-up periods

Table 3 contains the extracted data for the various treatment options used by the studies, alongside the corresponding treatment outcomes. One study had 45 patients, of which 15 received some form of treatment, but it did not correlate the specific treatments that led to a particular outcome.[2] As a result, we were unable to analyse data from that study in treatment efficacy. The follow-up period ranged between 1.5 and 40 months.

The authors found six articles that used botulinum toxin injection of various doses for treatment of first bite syndrome. These all resulted in complete resolution of symptoms.[23–26,28,31] Four articles found conservative management sufficient in allowing symptom resolution.[9,24,30,31] Topf *et al.*'s study found opioids and pregabalin to be effective treatments for first bite syndrome,[24] but Kesayan *et al.*'s study found medical treatments to be ineffective.[26] Various other treatment options were used, as listed in Table 4.

Quality of studies

Assessment of bias was performed using a recognised quality assessment tool, the details of which are shown in Table 5. Based on this quality assessment tool, two studies were rated poor,[25,31] three were rated fair[9,23,24] and one was rated good.[2]

Discussion

Botulinum toxin as treatment for first bite syndrome

Laccourreye *et al.*'s review suggested that botulinum toxin injections were the most effective first-line treatment option and found neuropathic pain medications to be ineffective.[10] Since their review, there have been five further studies which used botulinum toxin as a treatment; all patients with first bite syndrome included in these studies experienced complete resolution of symptoms. Various treatment doses and regimens were used. Doses ranged between 10 and 100 U, and injections tended to be repeated over 3–8 months.[23–26,28,31] Only one patient (in Ghosh and Mirza's study) did not require a repeat injection to achieve symptom resolution.[23] Three studies used a botulinum toxin A,[23,26,28] whereas the others did not specify the type of botulinum toxin used.[24,25,31] None of the studies reported any complications from the usage of botulinum toxin injection, even with higher doses of 100 U. Unfortunately, none of the studies included statistical analysis to demonstrate statistically significant outcomes in patients who received botulinum toxin for first bite syndrome.

Ali *et al.* was the first study to use botulinum toxin to treat first bite syndrome.[14] They used one injection of 75 U, which resulted in complete resolution of symptoms, a higher dose than the 11 U (repeated 3 successive times) used by Lee *et al.*, which resulted in partial improvement of symptoms.[19] In

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Table 4. Treatment options and outcomes of treatment grouped according to the articles included in the review

Treatment	Outcome	Authors
Botulinum toxin injection	Complete resolution	Sims and Suen,[25] Handa *et al.*,[31] Kesayan *et al.*,[26] Ghosh and Mirza,[23] Topf *et al.*,[24] Dubyk *et al.*[28]
Conservative	Complete resolution	Lammek *et al.*,[9] Handa *et al.*,[31] Topf *et al.*,[24] Gunter *et al.*[30]
Trigeminal nerve block and radiofrequency ablation	Temporary relief of symptoms	Kesayan *et al.*[26]
Medication	Opioids and pregabalin – effective	Topf *et al.*[24]
	Pregabalin, gabapentin carbamazepine, amitriptyline – ineffective	Kesayan *et al.*[26]
Acupuncture	Complete resolution	Fiorini *et al.*[27]
Laser tympanic plexus ablation	Complete resolution	Amin *et al.*[29]

Table 5. Results of quality assessment of case series studies based on the quality assessment tool for case series studies by the National Heart, Lung, and Blood Institute[22]

Criteria	Linkov *et al.*[2]	Lammek *et al.*[9]	Handa *et al.*[31]	Ghosh and Mirza[23]	Topf *et al.*[24]	Sims and Suen[25]
1. Was the study question or objective clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly and fully described, including a case definition?	Yes	Yes	Yes	Yes	Yes	Yes
3. Were the cases consecutive?	CD	CD	No	CD	CD	No
4. Were the subjects comparable?	Yes	Yes	CD	Yes	Yes	No
5. Was the intervention clearly described?	Yes	Yes	NA	Yes	Yes	Yes
6. Were the outcome measures clearly defined, valid, reliable and implemented consistently across all study participants?	Yes	Yes	No	Yes	No	No
7. Was the length of follow up adequate?	Yes	No	NR	No	No	No
8. Were the statistical methods well described?	Yes	Yes	NA	NA	NA	NA
9. Were the results well described?	Yes	Yes	No	Yes	Yes	No
Overall quality rating	Good	Fair	Poor	Fair	Fair	Poor

CD = cannot determine; NA = not available; NR = not reported

our review, Ghosh and Mirza was the only study which used the technique of low-dose botulinum toxin injections (10–40 U) at multiple sites in the parotid (2–7 sites) in 1 treatment session.[23] All the other studies used 1 injection of higher-dose botulinum toxin (≥50 U) at a single site.[24–26,28,31] Kesayan *et al.* initially used 50 U, which resulted in 75 per cent improvement in symptoms, followed by 65 U, which had complete resolution of symptoms.[26]

There is no clear consensus on the technique of using botulinum toxin to treat first bite syndrome. Single injections of a higher dose (50–80 U) or multiple lower-dose injections (10–40 U) have both been shown to be effective in achieving symptom resolution. One study specified the location of botulinum toxin injection as the point of maximal pain,[23] but the remaining studies did not define precisely the injection location.

The use of botulinum toxin as treatment for first bite syndrome is likely explained by its known mechanism of action. Botulinum toxin works by blocking acetylcholine release into the neuromuscular junction, leading to reduction in parasympathetic stimulation and weaker myoepithelial cell contraction in the parotid gland. This pathway is illustrated in Figure 2. Although there are theoretical complications, such as facial nerve paralysis or dry mouth secondary to inhibition of salivation, these have not been encountered in the literature. Sims and Suen suggested that this is because there are no neuromuscular junctions along the intraparotid neural pathway of the facial nerve, therefore it is unlikely that botulinum toxin will affect facial nerve function as a result of its mechanism of action.[25]

Conservative treatment of first bite syndrome

Our review identified four studies that showed that patients with first bite syndrome recovered without any form of treatment.[9,24,30,31] This was in addition to the four studies identified by Laccourreye *et al.*[10,13,16,18,20] Most of the cases analysed resolved within a few months to a year after a conservative approach to management. This suggests that if the pain is tolerated by the patient, using a watch and wait approach is a viable option. However, some form of treatment to relieve symptoms should be proposed if the pain is affecting the patient's eating habits and quality of life.

The authors have not found any explanation within the literature to explain the efficacy of conservative treatment. Based on the aetiology of first bite syndrome, it could be that the initial loss of sympathetic innervation to myoepithelial cells of the parotid gland recovers with time. This leads to less sensitivity to parasympathetic

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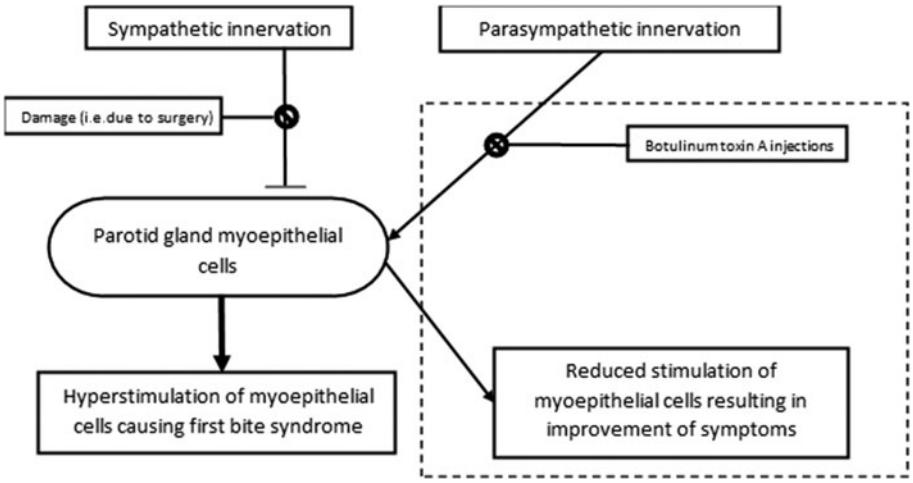

Figure 2. Hypothesised pathogenesis of first bite syndrome, with action of botulinum toxin type A injections as depicted in box with dashed border.

stimulation and thus no further hypercontractile response of the cells. However, this theory would be difficult to prove as no histological sample has been taken from the parotid glands of patients with first bite syndrome.

Other treatments for first bite syndrome

Apart from conservative treatment and botulinum toxin, the authors have identified a few other treatment methods, such as trigeminal nerve block, acupuncture and laser tympanic plexus ablation, to be effective in treating first bite syndrome.[26,27,29] Nonetheless, evidence of the effectiveness of these treatment options is lacking, and previous studies have shown tympanic neurectomy and acupuncture to be ineffective.[14,18] The same goes for medical treatments such as analgesia or anticonvulsants, which have contradictory findings in our review and the existing literature, although most studies have shown medications to be ineffective.[12–14,16,18,24,26] Previously, neoadjuvant radiotherapy was shown to be effective, but there have been no recent studies that used radiotherapy as treatment for first bite syndrome, likely due to the high morbidity related to it.[12,13,18]

Diagnostic criteria for first bite syndrome

First bite syndrome has been described by previous authors as a syndrome characterised by severe sharp or cramping pain in the parotid region that occurs with the first bite of mastication and improves with subsequent bites.[1,10] However, there are no established diagnostic criteria to assist clinicians in diagnosing this rare complication. Presentations of post-operative pain around the parotid or submandibular region might be confused with dental pain, temporomandibular disorders or other forms of facial neuralgia, which delays treatment for patients suffering from first bite syndrome.

By looking through all the articles included in this systematic review and in the literature, the authors have attempted to establish a diagnostic criterion for first bite syndrome to guide clinicians with diagnosis and to facilitate clarity in future research in this topic. The characteristics of the pain associated with first bite syndrome are listed in Table 6.

Table 6. Characteristics of pain associated with first bite syndrome as part of diagnostic criteria to aid with diagnosis

Nature of pain	Description
Site	Unilateral pain in parotid or retromandibular region (operated site and/or site of tumour)[9,10]
Onset	Sudden, acute onset[1,10]
Characteristic	Sharp pain[9]
Radiation	Most often radiating to the ear, less often to the neck or both[9]
Association	Begins during the start of mastication and diminishes with subsequent bites.[9] Can also be triggered during salivating or when thinking about food.[9]
Time and/or duration	Most often lasting a few seconds or <1 minute, but can last more than 5 minutes in certain cases[9]
Exacerbating factors	Worse with acidic foods[9,13]
Severity	Very severe pain affecting patient's desire to eat[9]

Limitations of studies included

The methodology and literature search design utilised in this review were comprehensive and based on robust guidelines. The inclusion and exclusion criteria were clear, and the article screening was corroborated by two independent reviewers. Thus, we believe this review presents a comprehensive analysis of treatments of first bite syndrome since 2013 and have confidence in our search strategy. The main limitations are related to the individual study designs of the papers included.

A key limitation in data reliability is the small sample population size analysed. First bite syndrome is a rare complication and the articles included reflect this, with small numbers of patients treated. The largest study, Linkov *et al.*,[2] included 45 patients, but the patient outcomes were not directly linked to an intervention therefore these patients were not included in analysis, which further reduced the total number of participants to 38.

The other main limitation was the study design and quality. Most of the studies were case reports and case series, level 6 evidence. None of the studies were blinded, placebo-controlled

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interventional studies, therefore we are limited in the conclusions that can be drawn. The studies included failed to provide relevant statistical analysis of results that may aid appropriate interpretation. There was also high variation in dosage, frequency and site of medication administration between studies, which made drawing a unifying conclusion difficult. This heterogeneity hampers our ability for direct comparison or meta-analysis.

In the studies included where botulinum toxin was used to treat first bite syndrome, most patients experienced recurrence of symptoms after a certain period, after which a repeat injection was required. Ghosh and Mirza noted that in between their four-monthly follow-up visits, patients reported symptom recurrence with the same level of intensity as the initial episode.[23] The pattern continued until the symptoms eventually resolved for good. This phenomenon, along with the fact that first bite syndrome symptoms also tended to resolve independently with conservative management, gives rise to the question of whether botulinum toxin alters the natural history of the condition and enhances recovery. It could be hypothesised that botulinum toxin only serves as symptomatic relief while the condition runs its self-limiting course. A good-quality randomised, controlled trial would go some way to improving our understanding of therapeutic approaches to this phenomenon, but we recognise the practical challenges this would pose in a patient group seeking immediate symptomatic relief.

Recommendations

Because of the lack of high-quality studies, the authors are only able to make a cautious recommendation of an overall treatment approach for patients with first bite syndrome. Clinicians encountering patients with first bite syndrome may consider conservative treatment for patients for a period of 6–12 months if the pain can be tolerated by patients without significantly affecting their quality of life. Otherwise, although there has been no demonstration of statistically improved outcome, botulinum toxin injections appear to be effective for symptom management, which will need to be repeated as required until complete symptom resolution. Unfortunately, there is a lack of evidence to recommend the dose, frequency or site of injection. Treatment options such as acupuncture, medications including analgesia or anticonvulsants, or trigeminal nerve block lack sufficient evidence for authors to recommend their use in treatment for first bite syndrome.

Conclusion

As identified in this review, there have been more recent published articles about the efficacy of various treatments for first bite syndrome in the past 10 years. Some studies have found that symptoms eventually resolve with conservative management, and other studies have found botulinum toxin to be effective for symptom resolution, although this improvement was not statistically proven. Unfortunately, there is no established technique including dose, frequency or site of injection. Other treatment options lack robust evidence to justify their application. All evidence found was of insufficient quality.

As discussed, there are various limitations in the conclusions we can draw from the data available. Higher-level evidence would help in further understanding this topic, and the 'gold standard' recommendation is a high-quality placebo-controlled, double-blinded randomised, controlled trial. However, this brings logistical, financial and ethical challenges, especially for a rare complication such as first bite syndrome. The authors therefore suggest the formation of a national registry to support data collection and subsequent further research into this topic.

- Six new studies were identified that have found botulinum toxin injections to be an effective treatment for first bite syndrome, affirming findings from the previous review, but these outcomes are not statistically proven
- Conservative treatment can be trialled initially as some studies have shown symptoms improve with time, a finding not identified from the previous review
- There is a lack of evidence of efficacy for neuropathic pain medications for first bite syndrome, which correlates with findings from the previous literature review
- Case reports were identified that describe novel methods, such as acupuncture or tympanic plexus ablation, that are effective for first bite syndrome
- Cautious recommendations for patients suffering from first bite syndrome are made, for example conservative treatment could be trialled initially and botulinum toxin injections performed if the symptoms do not improve
- A form of national registry to gather sufficient data into this research topic would be useful because of the logistical and ethical challenges in carrying out a high-quality randomised, controlled trial for first bite syndrome patients.

Competing interests. None declared.

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