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Botulinum Toxin A in the Management of Pediatric Sialorrhea: A Systematic Review

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Abstract

Objective: Botulinum toxin A is known to be effective and safe in managing sialorrhea in pediatric patients; however, there is no consensus on a protocol for optimal injection sites and appropriate dosing for injection.

Methods: This review was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol. PubMed, EMBASE, and other databases were queried to identify articles that evaluated botulinum toxin type A for the treatment of sialorrhea in the pediatric population. A total of 405 studies were identified. After applying inclusion and exclusion criteria, 31 articles were included for review.

Results: A total of 14 studies evaluated 2-gland injections, and 17 studies evaluated 4-gland injections. Of the 31 studies included, one study assessed incobotulinumtoxinA (Xeomin®) the remaining all used onabotulinumtoxinA (Botox®). For 2-gland injection studies, a combined total of 899 participants were reviewed, where 602 participants received 50 units into their submandibular glands, while 262 participants received 30 to 50 units. Among 4-gland injection studies, there was a combined total of 388 participants, with the most prevalent dosage utilized being 60 to 100 units in 230 participants, followed by 100 units total in 77 participants. The most common adverse event was dysphagia which resolved in nearly all cases. Three studies aimed to examine 2-gland versus 4-gland injections, with 2 of the studies concluding 4-gland injection was superior.

Conclusions: The strength of evidence suggests that the dosing of 50 units total of onabotulinumtoxinA to the submandibular glands is safe and effective in the pediatric population. For 4-gland injections, bilateral submandibular and parotid gland injections of 60 to 100 units total is the safe and effective dosage. There is no substantial evidence comparing 4-gland injections to 2-gland injections, but research thus far suggests 4-gland injections to be superior. Future study is needed to evaluate incobotulinumtoxinA and abobotulinumtoxinA dosages in the pediatric population.

Keywords

salivary gland, sialorrhea, botulinum toxin A, pediatric, submandibular gland, parotid gland

Introduction

Sialorrhea, or excessive drooling, is the unintentional loss of saliva or other oral cavity contents due to the lack of coordination of the orofacial and neck musculature. This condition affects many patients and can severely impact their health and quality of life. Saliva is produced and secreted by 6 major salivary glands (parotid, submandibular, and sublingual glands bilaterally) as well as hundreds of minor salivary glands. When the salivary glands are unstimulated, the submandibular and sublingual glands contribute 70% of salivary sections; however, the parotid gland provides the most saliva when stimulated.[1] Drooling is normal in children under the age of 4 but thereafter is considered problematic. Sialorrhea is a common condition in pediatric patients with intellectual disability, cerebral

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palsy, autism, and patients who experience other neuromuscular or sensory dysfunction. The most common cause of sialorrhea in the pediatric population is cerebral palsy, with a reported 10% to 58% incidence.[2] The etiology of sialorrhea is broad, including neuromuscular and sensory dysfunction, hypersecretion of saliva, anatomic abnormalities, such as macroglossia and orthodontic problems, and medications, such as anti-seizure medications.[3] The underlying mechanisms of sialorrhea can be attributed to hypertrophied salivary glands, increased saliva production, and incomplete deglutition mechanism due to a lack of neuromuscular control of the oral musculature. The complications of sialorrhea include perioral chapping, secondary infection of perioral skin, dehydration, increased risk of aspiration pneumonia, foul odor, reduced hygiene, interference with speech, and psychosocial issues such as low self-esteem and social isolation.[3,4] Although the complications are not life-threatening, the physical and psychosocial implications for both the patient and caregiver can negatively impact the quality of life.[5]

The efficacy of chemodenervation of salivary glands with BoNT was first demonstrated by Pal et al[6] in 2000 in patients with Parkinson's disease and noted significant improvements in these patients. This study propagated further advancements in the safety and efficacy of BoNT-A in treating sialorrhea through various case studies, retrospective studies, open-label trials, and controlled clinical trials. Jongerius et al[7] presented the first case series of BoNT injections in 3 children with cerebral palsy and demonstrated a reduction in salivary secretion. OnabotulinumtoxinA (Botox®, Allergen) is the most common toxin used for chemodenervation of salivary glands, but other neurotoxins that have been approved include abobotulinumtoxinA (Dysport®, Ipsen Biopharm Limited), incobotulinumtoxinA (Xeomin®, Merz Aesthetics), and rimabotulinumtoxinB (Myobloc®, Supernus Pharmaceuticals).[8,9] The botulinum neurotoxin (BoNT) is produced by the *Clostridium botulinum bacterium* and functions by inhibiting acetylcholine's presynaptic release at the neurosecretory junctions within the salivary glands, thus inhibiting parasympathetic production and secretion of saliva. BoNT-A specifically inhibits a protein called SNAP-25, which regulates acetylcholine release into the neuromuscular junction by fusing vesicles containing acetylcholine with the plasma membrane.[10]

The side effect profiles of neurotoxin injections are generally fewer and more tolerable than anticholinergic medication, including dry mouth, saliva thickening, and salivary gland swelling.[11] Diffusion of toxin into adjacent musculature can cause chewing difficulties and transient weakness of mouth closure; however, this is less common with ultrasound guidance for injection.[12] Multiple studies have established the safety and efficacy of ultrasound-guided botox injections by ensuring injection accuracy.[10,13,14] Image guidance provides proper positioning of the needle inside the salivary gland, enables visualization of anatomic variations, and decreases iatrogenic injury to adjacent structures. One study demonstrated a 41% rate of adverse events following non-image-guided injections.[15] If conservative management fails to improve the sialorrhea, then consultation for surgical ligation of salivary ducts or surgical excision of salivary glands is appropriate.

The literature has shown the efficacy and safety of neurotoxin injections in controlling sialorrhea; however, clear protocols on neurotoxin injections are not well described. Specifically, there is no consensus on which salivary glands should be injected (parotid, submandibular, or both) and optimal dosing in the pediatric population. In addition, there is significant heterogeneity in the number of glands treated and mixed dosing protocols, which presents a challenge for providers seeking an effective, evidence-based protocol for injections. Therefore, this systematic review aims to determine in the pediatric population (1) determine the optimal dosing and injection site of neurotoxin treatment for sialorrhea and (2) provide a neurotoxin treatment protocol for sialorrhea.

Methods

Literature Search

This study used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) process. A systematic review following the PRISMA checklist was conducted, and the following databases were searched: Medline via PubMed, The Cochrane Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), and EMBASE databases for potential reports in English. The full search criteria and terms are outlined in Supplemental Figure 1. There was no date restriction on any of the searches. Additional references were obtained from a manual cross-bibliography search within the retrieved articles.

Selection Criteria

All randomized controlled trials, controlled clinical trials, prospective cohort studies, retrospective cohort studies, and case series were identified. Inclusion criteria included (1) all reports on the pediatric population, defined as ages 0 to 21 years of age, with sialorrhea due to any etiology, (2) interventions that used any type of BoNT-A, including onabotulinumtoxinA, abobotulinumtoxinA, and incobotulinumtoxin A, in efforts to reduce or resolve sialorrhea in the pediatric population, (3) all intervention settings, as well as all types of providers administering the neurotoxin, and (4) studies with any dosing, frequency of injections, injection site location, ultrasound-guidance with injection, and anesthetic used. Furthermore, studies were only included if there were quantifiable outcomes.

Studies were excluded if (1) they did not discuss neurotoxin use for sialorrhea in the pediatric population, (2) if they discussed botulinum toxin type B, including rimabotulinumtoxinB (MyoBloc® and NeuroBloc®), (3) were limited to intraductal neurotoxin injections, (4) did not use ultrasound guidance with injection, (5) did not differentiate between the pediatric and adult population, and (6) meta-analyses and systematic reviews. Additionally, studies that did not have specific dosages were excluded.

Data Extraction

Each study's eligibility was evaluated independently by 3 reviewers (S.P., T.H., and K.Z). Discrepancies in article inclusion were resolved via discussion amongst the authors to achieve consensus with input from the senior author (J.L.). The studies were assessed for eligibility based on their titles and abstracts in the first phase, excluding irrelevant studies. In the second phase, the studies were evaluated for eligibility based on their full text. Information collected included author, year of publication, type of study, number of patients, botulinum toxin type, population characteristics, type of gland injected, the dose of toxin injected, outcome measures, and adverse effects. The Oxford Center for Evidence-Based Medicine was used to determine the level of evidence of each study within our systematic review.

Results

Description of Studies and Study Participants

A total of 405 unique abstracts were identified, of which 120 met the initial screening criteria. After a full-length review of articles, an additional 89 articles were excluded for the reasons outlined in Figure 1 (PRISMA). Thus, a total of 31 studies met inclusion criteria for our systematic review. The included studies ranged from 2001 through 2020. There were 5 randomized clinical trials, 15 prospective studies, 7 retrospective studies, and 4 case series/reports. A total of 14 studies evaluated 2-gland injections (either parotid or submandibular glands bilaterally) with a combined total of 899 participants reviewed. For 4-gland injections (bilateral parotid and submandibular glands), 17 studies were evaluated with a combined total of 388 participants reviewed. All studies are further described in Supplemental Table 1.

Of the 31 total studies, 15 studies evaluated drooling in children with cerebral palsy specifically or combination with an unspecified intellectual disability,[7,13,16-28] 14 studies evaluated drooling in patients with a variety of neurologic or neurodevelopmental impairments,[10,14,29-40] 1 study looked at hypersalivation in spinal muscle atrophy type I,[41] and 1 study involved a case series with Rett syndrome.[42] The age range was 1 month old to 21 years old.

Level of evidence. The Oxford Center for Evidence-Based Medicine was used to determine the level of evidence of each study within our systematic review. The level of evidence for 2-gland injection studies included 11 level 3 studies, 2 level 4 studies, and 1 level 5 study. The level of evidence for 4-gland injection studies included 5 level 2 studies, 11 level 3 studies and 1 level 4 study.

Objective and Subjective Measures

Despite decades of research on sialorrhea, there is no established consensus on assessment tools for measuring the effectiveness of interventions for sialorrhea. In our review, the following objective outcomes were used to measure sialorrhea quantitatively: salivary weight in grams over a specified period of time, drooling quotient, salivary flow rate, and the number of bib changes per day. Drooling quotient and the salivary flow rate were the most frequently used objective measures, each reported in 7 studies. Subjective measures used in these studies included the Drooling Impact Scale (DIS), Drooling Frequency and Severity Scale (DFSS), patient and caregiver visual analog scale (VAS), and Teacher Drooling Scale (TDS). DFSS and VAS were the most frequently used subjective measures, each reportedly used in 6 studies. Overall, the majority of studies (23 of 31) used multiple methods for assessment. The heterogeneity of these outcome measures and variability in measurement times prevent a comprehensive analysis of efficacy.

Dosing of BoNT-A

Injection sites varied amongst the included studies. A total of 14 studies evaluated 2-gland injections (either parotid or submandibular glands bilaterally),[7,13,14,16-21,29-33] and 17 studies evaluated 4-gland injections (bilateral parotid and submandibular glands).[10,22-28,34-42] The neurotoxin utilized in 30 studies was onabotulinumtoxinA (Botox®, Allergen), and 1 study evaluated incobotulinumtoxinA (Xeomin®, Merz Aesthetics).[42] The total injection dose was weight-dependent in 8 studies, with children weighing <15 kg receiving 30 total units, 15 to 25 kg receiving 40 total units, and >25 kg receiving 50 total units, on average.[7,20,24,25,31,33,37,41] Bernardo et al[42] conducted the only study that used Xeomin® for injections. The authors injected bilateral submandibular and parotid glands with a total dose of 150 units and found a statistically significant reduction in sialorrhea, with no adverse effects reported.[42]

For 2-gland injection studies, a combined total of 899 participants were reviewed, where 602 participants received 50 units into their submandibular glands,[7,16-18,32] while 262 participants received 30 to 50 units.[7,13,19-21,29-31,33] Two studies reported dosages outside the 30 to 50 unit range.[14,33] Van Hulst et al[33] reported 8 children received dosages >50 units total to submandibular glands. Three participants received an unknown dose. Hassin-Baer et al[14] injected 15.5 units

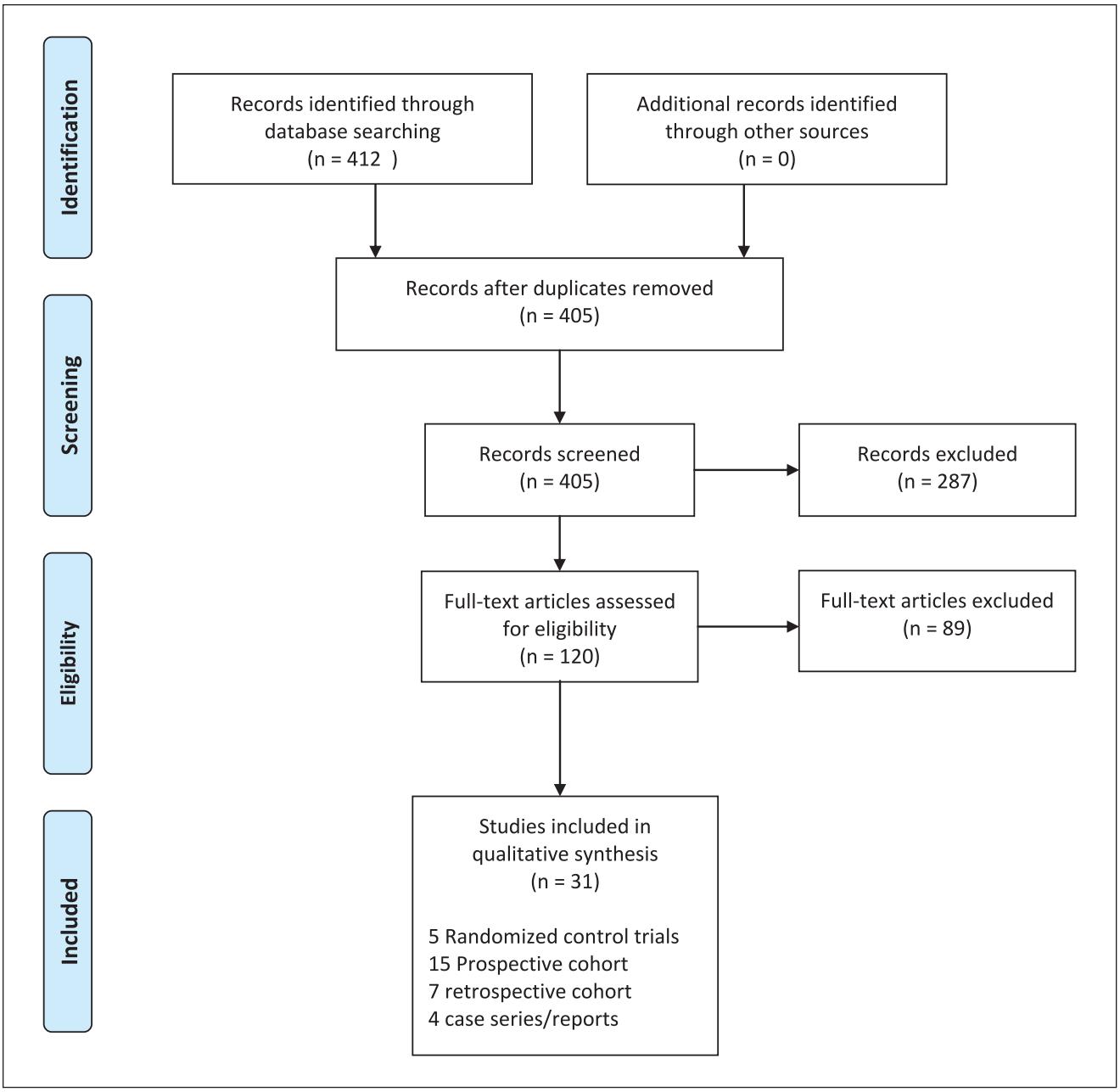

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram.

total bilaterally into the parotid glands of 9 participants. A total of 8 participants subsequently received a booster injection 1 month following the first injection. Suskind and Tilton compared 2-gland versus 4-gland injections, where 12 participants received 30 units total or less into the submandibular glands.

Among 4-gland injection studies, a combined total of 388 participants received onabotulinumtoxinA with an extensive range of dosages. The most prevalent dosage was 60 to 100 units total in 230 participants.[22,23,28,34,36,37,39,40] The second most prevalent dosage was 100 units total in 77 participants.[24,26,27,36,38,41] Khan et al conducted the only study that used greater than 100 total units of BoNT-A for 4-gland injection in 45 patients. On the contrary, a total of 36 participants across the 4-gland studies received less than 60 units of BoNT-A total.[10,25,34,41]

Two-Gland Versus Four-Gland Injection

Three studies aimed to examine 2-gland versus 4-gland injections.[22,27,28] Suskind and Tilton[22] included 22 participants in the study, with 12 receiving injections in the submandibular

gland alone and 10 receiving bilateral submandibular and parotid gland injections. Those who had only a submandibular gland injection (2-gland) had a successful response in 33% of participants, while 80% were considered responsive in those who received submandibular and parotid gland injections bilaterally (4-gland).[22] Likewise, Møller et al had 14 participants who received a dose elevation protocol and were found to have the best outcomes with 4-gland injections.[28] Nordgarden et al[27] injected 100 units total to 4 glands in 5 participants, and 1 participant received submandibular gland injections alone, but they reported side effects of dysarthria, dysphagia, and increased salivary viscosity, ultimately leading to study termination.

Adverse Effects

Although adverse reactions to BoNT-A injections are rare, 14 studies reported 1 or more adverse events following injection, and 1 randomized-controlled trial was terminated due to serious adverse events.[27] Specifically, Nordgarden et al terminated their study early due to one participant, who weighed 33 kg before treatment, developed severe dysphagia, leading to poor intake of food and fluids and loss of 4 kg over 2 weeks.[27] The most significant adverse events reported include severe dysphagia requiring hospitalization for aspiration pneumonia.[27,35] One patient in a study received 3 treatments of BoNT-A for sialorrhea, and developed aspiration pneumonia following each subsequent treatment.[35] Other reported adverse events include xerostomia, mild-to-moderate dysphagia, dysarthria and speech difficulties, coughing, chewing and feeding difficulties, saliva thickening, and weakening of oral musculature.[7,19,24,30,33,35-40] These adverse effects were transient, managed conservatively, and resolved within days to weeks with no long-term sequelae.

Discussion

Botulinum toxin A has been established as a safe and effective modality in treating sialorrhea in the adult and pediatric population; however, it remains challenging to manage. Research has demonstrated that ultrasound guidance is superior to landmark usage, but there has yet to be an established protocol on dosing and gland injection sites. To date, our systematic review is the most extensive evaluation of dosing in the pediatric population. It is important to emphasize the heterogeneity of the pediatric population with sialorrhea, various injection techniques amongst institutions, and non-uniformity of outcomes measures used to assess the efficacy of BoNT-A injection across all studies that preclude a formal meta-analysis. Additionally, the optimal dosing of BoNT-A is difficult to assess due to the wide range of doses used throughout multiple studies; however, the effect of BoNT-A appears to be dosage-dependent. Low doses have been shown to result in a sub-therapeutic effect requiring re-injection. For example, Hassin-Baer et al injected a mean dose of 15.5 units total depending on body weight.[14] Eight out of 9 patients required a booster injection 1 month after the first injection. On the contrary, a supra-therapeutic dose (>100 units) of BoNT-A can result in unwanted side effects such as severe dysphagia.[35]

The majority of the articles found had the primary focus of determining efficacy and safety of chemodenervation of salivary glands, but through data extraction and level of evidence analysis, dosage recommendations may be made. For 2-gland injections, given that all the studies except one were Category 3 and 4, the strength of evidence suggests that the dosing of 30 to 50 units total of onabotulinumtoxinA to the submandibular glands is safe and effective in the pediatric population. For 4-gland injections, there were 64 participants that received BoNT-A injections in the level 2 studies. Of the 64 participants, 48 received 80 to 100 units of BoNT-A, and results demonstrated this dosing was safe and effective in the patient population. The level 3 studies demonstrated 234 participants received 60 to 100 units of Botulinum A with no significant rates of complications. Given this strength of evidence, we recommend for bilateral submandibular and parotid gland injections that 60 to 100 units total but likely 80 to 100 units total is the safe and effective dosage in the pediatric population. Though rare, providers should always monitor for concerning adverse effects.

This systematic review aimed to provide dosage recommendations for all 3 botulinum toxin A toxins available; however, this study elucidates the lack of research on using abobotulinumtoxinA incobotulinumtoxinA in the pediatric population for sialorrhea management. There were no studies identified that used abobotulinumtoxinA and only one study using incobotulinumtoxinA by Bernardo et al[42] with only 5 patients. Further research is warranted given this is a category 3 study with a small sample size. One double-blind placebo control study conducted by Alrefai et al[43] demonstrated that 100 to 140 units of abobotulinumtoxinA were safe and effective in the pediatric population; however, this study ultimately did not meet inclusion criteria. Caution should be used by providers with the alternative toxins, although reassuring that adult populations have little to no adverse effects with their usage.

There is little research comparing 2-gland and 4-gland injections, but we identified 3 randomized control studies, of which 2 concluded that 4-gland injections were safe and the most effective.[22,27,28] Although we should note the small sample sizes in Suskind and Tilton's[22] and Møller et al's[28] studies. Alternatively, Nordgarden et al had only 6 participants receive treatment before terminating the study due to adverse effects. Thus, while the current research is promising that 4-gland injection may be superior to 2-gland injection, further research would be beneficial.

While it is reassuring, most of the studies did not have any reported major complications regarding adverse effects. Of those that reported major complications, dysphagia was the most common. This complication is likely due to toxin diffusion into adjacent musculature and soft tissue leading to consequent muscle weakness. While this is a concerning complication, consideration for the patient population and their comorbidities may be considered. Dysphagia is a common occurrence in this population, and an aspect of sialorrhea is the poor ability to swallow and manage secretions. Therefore, it is difficult to state definitively that the BoNT-A injections were the cause of dysphagia. Van Hulst et al[32] and Erasmus et al[19] hypothesized that children who experience thickened saliva following injection are most at-risk for worsening dysphagia likely due to thickened saliva complicating pre-existing difficulty with swallowing. A full evaluation of the concern must be completed if patients report dysphagia to ensure we are not stopping a beneficial intervention needlessly.

While the focus of our study was not the assessment of the measurement tools used to determine outcomes of sialorrhea management, the review helped to demonstrate the lack of consensus on the matter. A wide range of assessments used both objective and subjective, and most studies used a combination of assessments to determine efficacy. Due to the heterogeneity of the outcome measures utilized and the wide range of dosages, our ability to define a protocol in performing chemodenervation of the salivary glands is limited, as a meta-analysis could not be completed. Indeed, future investigation is warranted to evaluate the most effective and well-tolerated measurement tool for the pediatric population as this will help ensure validity and reliability of determining outcomes and establish an appropriate protocol.

Conclusion

The systematic review aimed to establish safe and effective dosages and injection sites and a protocol for chemodenervation of the salivary glands for sialorrhea in the pediatric population. Currently, there is no substantial evidence regarding 4-gland injections compared to 2-gland injections. However, our study demonstrates that 2-gland injections with onabotulinumtoxinA into the submandibular gland are safe and effective at a total injection dose of 30 to 50 units. Four-gland injections are safe and effective at dosages totaling 60 to 100 units. Due to heterogeneity in interventions and outcome measures, a meta-analysis was unable to be completed to ascertain an optimal dosing protocol.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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