Botulinum toxin usefulness in the treatment of drooling in childhood.

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Abstract

Sialorrhea is defined as the involuntary excess of saliva in the mouth that exceeds the lip margin. This is not due to excessive saliva production but also to an alteration in the process of oral secretions that occurs mostly in people with neurological damage. Among the pathologies that can be treated with sialorrhea are Parkinson’s disease, cerebral palsy, stroke, amyotrophic lateral sclerosis or facial paralysis, among others. It is a disabling symptom which, although sometimes is unnoticed and not always recorded, can lead to significant medical problems. Complications include the appearance of cavities, persistent cough, difficulty in eating, dermatitis, skin infections due to Candida Albicans or Staphylococcus Aureus caused by persistent humidity, and even recurrent pneumonia and aspiration. Furthermore, it has been proved that it harms the patient social life, causing alterations in speech and diminishing their quality of life, sometimes even leading to social isolation.

For the therapeutic management of sialorrhoea, there are currently different treatment alternatives. Oral motor training is postulated as a type of conservative therapy that, although it does not completely stop sialorrhea, can reduce its clinical severity. Functional management is considered to be beneficial especially when is performed concomitantly with other types of treatment. However, these techniques have limited evidence and requires a capacity for understanding and patient participation that is not possible in all cases. Pharmacological treatments, such as anticholinergics (glycopyrrolate or atropine), are the most widely used drugs, due to their mechanism of action: they block the parasympathetic innervation of the salivary glands. However, the reduction of side effects such as tachycardia, confusion, or urinary retention after taking this medication is not negligible. Other invasive techniques include radiotherapy of the salivary glands or surgery to remove the glands, ligation of the duct, or neurotomy of the tympanic nerve. This type of treatment, as it obtains irreversible results, is usually carried out when all other therapies fail. Currently, botulinum toxin is one of the most commonly used therapeutic procedures for the treatment of sialorrhoea. Although its aesthetic use has historically been the best known, in recent years its therapeutic use has been consolidated by being introduced in numerous pathologies such as focal spasticity, dystonia or facial paralysis. It is a powerful neurotoxin, produced by the bacterium Clostridium, Botulinum, which reduces sialorrhoea by inhibiting the release of acetylcholine in the cholinergic neurosecretory junction of the salivary glands. The main objective of our study was to evaluate the efficacy of the treatment with botulinum toxin type A infiltrations under ultrasound control in children with sialorrhea treated at our Rehabilitation Unit between 2009 and 2019 and to analyse the factors associated with better results of the technique.

Keywords: Sialorrhea, Botulinum.

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Introduction

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For the therapeutic management of sialorrhea, there are currently different treatment alternatives. Oral motor training is postulated as a type of conservative therapy that, although it does not completely stop sialorrhea, can reduce its clinical severity. Functional management is considered to be beneficial especially when is performed concomitantly with other types of treatment. However, this technique has limited evidence and requires a capacity for understanding and patient participation that is not possible in all cases.

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Currently, botulinum toxin is one of the most commonly used therapeutic procedures for the treatment of sialorrhea. Although it’s aesthetic use has historically been the best known, in recent years its therapeutic use has been consolidated by being introduced in numerous pathologies such as focal spasticity, dystonia or facial paralysis. It is a powerful neurotoxin, produced by the bacterium Clostridium Botulinum, which reduces sialorrhoea by inhibiting the release of acetylcholine in the cholinergic neurosecretory junction of the salivary glands [6-8].

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Materials and Methods

A retrospective, analytical, observational study was conducted on a paediatric cohort subjected to botulinum toxin ultrasound-guided injections for the treatment of severe sialorrhea.

Inclusion criteria
- Ultrasound-guided botulinum toxin injections performed on paediatric patients diagnosed with severe sialorrhea in our Rehabilitation Unit between 2009 and 2019.
- Signature informed consent.

Exclusion criteria
- Botulinum toxin injection of the facial-cervical area for a cause other than sialorrhea.
- Absence of follow-up at 30 days after the injection.

Data recorded
1. Demographic data: Age, sex, underlying pathology (congenital anomalies, acquired neurological disorders, or acquired non-neurological disorders).
2. Intake of drugs that could alter the saliva production and management such as glycopyrrolate, atropine, or scopolamine.
3. Number of glands (2 or 4) and which ones were injected (parotid glands, submandibular glands, or both).
4. Total dose of botulinum toxin used.
5. Evaluation of the efficacy of the treatment by
   a. Objective analysis: Reduction in the number of bibs/tissues before and 30 days after treatment, considering clinical improvement a reduction of 50%.
   b. Subjective analysis: Drooling Severity and Frequency Scale before and 30 days after treatment (taken from Crysdale and White and modified by Aguilar-Rebolledo) [9].

Severity
1. Dry: never drools.
2. Mild drooling: only lips wet.
3. Moderate drooling: drool reaches the lips and the chin.
4. Severe drooling: drool drips off chin and onto clothing.
5. Profuse drooling: drooling off the body and onto objects.

Frequency
1. No drooling.
2. Occasionally drools.
3. Frequently drools.
4. Constantly drools.
5. Use of general anesthesia.
6. Side Effects (SE) presence throughout the 30 days following the injection.
   - SE secondary to the procedure: pain, hematoma, bleeding, infection, facial nerve trauma.
   - SE secondary to the toxin: masticatory muscle weakness, dysphagia, xerostomia, thick saliva, intravascular injection.

8. Ways of feeding: oral, non-oral (nasogastric tube, PEG), or mixed.

Procedure

Botulinum toxin type A was used in all cases. The dose depended on the child's weight-based in the hospital protocol:
- In patients with body weight <25 kg: 1.4 IU per kilogram in case of parotid glands and 0.6 IU per kilogram in case of submandibular glands.
- In patients with body weight >25 kg: 25 IU per gland.

The patients were in a supine position on a stretcher with the Rehabilitation Physician who performed the technique and the ultrasound equipment on the right side of the patient. The patient's head was lateralized to one side or the other depending on the gland to be injected. It was necessary to use distractors such as sounds, videos or drawings, and head and limb fastening by family members or Nursing Assistants. In cases where the infiltration was impossible to perform in the consultation room, due to lack of cooperation by the patient, it was performed under general anaesthesia.

A Mindray type ultrasound machine with a linear L14-4s probe was used to locate the glands. For the parotid gland, the probe was placed parallel to the descending mandibular branch, 1 cm...
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from the facial nerve, injecting in a single out-of-plane point. The submandibular gland was located by placing the probe perpendicular to the angle of the lower jaw, visualizing it as a triangular structure of different echogenicity, and the infiltration was performed out-of-plane.

Botulinum toxin vials were diluted with 1cc of saline solution (0.5%). The injection was performed under aseptic conditions with Chlorhexidine (0.5%) using 1 ml syringes and 0.5 mm × 25 mm (25 G × 1) and 0.5 mm × 16 mm (25 G × 5/8") needles.

The selection of the gland to be injected (parotid glands, submandibular glands, or both) was individualized according way of feeding and the location of the largest amount of saliva, as well as what time of day drooling was most frequent and more intense. If it was increased during eating and drinking the glands of choice would generally be the parotid glands, while the excess of drooling at rest would correspond to major submandibular gland participation.

A statistical analysis of the data was carried out using SPSS statistics, version 20. The Wilcoxon test was used for the comparison of means of the severity and frequency scales before and at 30 days after treatment. The Mann-Whitney U-test compared the reduction in the number of bibs among patients undergoing injections under sedation and without sedation, and according to the number of glands infiltrated. The Kruskal-Wallis test was used to compare the reduction of the number of bibs according to the type of gland injected and the patient type of feeding. To analyse the association between the way of feeding and the glands injected, a Chi- Squared test was performed.

Results

Sixty-seven patients were treated, (28 males/39 females) (Figure 1). 31 were Cerebral Palsy patients, 22 had a congenital pathology, and 14 had a developmental disorder with psychomotor retardation (Figure 2). The mean age of the sample was 9.03 (range 4-14 years).

![Figure 1. Gender.](image_url)

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The submandibular gland was the most frequently injected, representing 53.7% of the total procedures. Although the Botulinum Toxin average total dose was 53.78 IU (SD 21.43). When we calculated the amount of toxin used on each gland, we described a parotid and submandibular mean dose of 23.06 IU (SD 4.94), and 19.49 IU (SD 5.02), respectively.

65.7% of patients presented severe drooling on the pre-treatment severity scale, while 7.5% presented moderate drooling and 26.9% profuse drooling. 30 days after the treatment: 6% presented no drooling whatsoever, 34.3% mild drooling, 34.3% moderate, 20.9% severe, and 4.5% profuse (Figure 3).

![Figure 3. Pre-post treatment severity scale.](image_url)

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In terms of the Drooling Frequency Scale before treatment: 11.9% of participants frequently drooled, while 88.1% constantly drooled. 30 days after the treatment: 3% of patients reported no drooling, 34.3% occasionally, 31.3% frequently and another 31.3% constantly (Figure 4).

![Figure 4. Pre-post treatment frequency scale.](image_url)

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To compare the means of the Drooling Severity scale before and after 30 days of treatment, the Shapiro-Wilk test was
applied to check the normality of the data and non-parametric tests were carried out on those data that did not follow a normal distribution. Statistically significant differences were obtained when comparing means with a p<0.05 to 95% CI.

Likewise, when comparing the means of frequency scale for the sample of individuals, statistically significant differences were obtained with a p<0.05 to 95% confidence. Moreover, we compared the reduction in the number of bibs/garments in patients injected under general anesthesia with patients without it. A p=0.176 (p>0.05) was obtained in this test, so we accept the equality of means between both groups. We also compared the reduction in the number of bibs/garments according to glands injected (parotid glands, submandibular glands, or both). We obtained a p-value of 0.758 (>0.05) so we accept that there is no statistically significant difference in the reduction in the number of bibs/garments according to the glands selected to be injected.

Similarly, the improvement of drooling by the reduction in the number of bibs/garments according to the number of glands injected (2: parotid or submandibular, or 4: 2 parotid and 2 submandibular) was analyzed. We obtained a p-value greater than 0.05 so we accept the equality of means between groups. We studied whether there is a relationship between which glands are injected and the way of feeding the patient does too. We observed a p-value <0.05 so we assume that there is an association between the type of feeding the patient does and the type of injected glands.

In the same way, to check whether there were differences in the effect of the treatment according to the way of feeding, in the reduction of the number of bibs/garments, we obtained a p-value of 0.773 (>0.05), so we accept that there is no statistically significant difference in the reduction in the number of bibs/garments with the treatment according to the way of feeding the patient does.

In addition to this, the mean reduction in the number of bibs/ garments was 48%. 10 participants did not get any result, and 4 patients got worse, increasing the number of bibs/garments (2 by 25% and 2 by 50%).

On top of that, the efficacy of the treatment evaluated with the reduction in the number of bibs/ garments was compared between the three groups of pathologies. To test the assumption of normality, we applied the Shapiro-Wilk test, and then we compared the means of three groups with the ANOVA test. No statistically significant differences were found between the reductions in the number of bibs/garments according to the pathology. Finally, side effects data were gathered from the total number of treatments. The only injection-related adverse effect was subcutaneous hematoma in one patient, whereas mild dysphagia was reported by one patient as the only BoNT related side effect.

Discussion

The results of our survey confirm that the ultrasound-guided injections of botulinic toxin type A are an effective treatment for patients suffering from severe sialorrhea. Although more and more articles in the literature support the use of this therapeutic option as a reliable alternative treatment [1-2], there is currently no agreement on how to perform the technique and the total dose to use.

The results observed in our study show significant decreases in the intensity and frequency of sialorrhea and the number of bibs used, with an average total dose of the toxin of around 50 IU, contrary to what is recommended in other publications [8-11]. A dose adjustment was performed according to an internal protocol based on the patient's weight, however, when the infiltration was only performed in two glands, the final dose was rounded up, above the weight-adjusted value. Our aim was always to individualize the technique. However, we cannot compare these circumstances with other publications since the dose adjustment in them does not follow such individualization.

Recent publications have proposed the infiltration of the four major salivary glands for the treatment of excessive sialorrhea as the most effective method. However, the possibility of infiltrating two glands selectively and individually from the patient has not been assessed. After reviewing the current scientific literature, there are no studies that relate the selection of the gland to be infiltrated with the amount and/or localization of the saliva or the type of feeding the patient receives. Under basal resting conditions, the submandibular glands are responsible for 70% of saliva production, while the parotid glands increase their share in secretion by five when faced with a stimulus such as food or drink. We could speak of a predominance of parotid glands if this is intensified during or after meals, is accumulated in the lower vestibule, and it is more frequent in patients who take oral food. In this way, sialorrhea with greater participation of submandibular glands would be one where the symptomatology is predominant at rest and the saliva is mostly located on the floor of the mouth and may prevail in patients with non-oral feeding.

Thus, in our revision we found that there were no statistically significant differences in the degree of decreasing of sialorrhea between patients who were infiltrated with two glands (parotid or submandibular) and patients who were treated with all four glands, being too similar in both situations. These results are in opposition to studies such as Mazlan et al. [11], and Fuster et al. [12], where the superiority of the combined treatment was observed in all four glands. Thus, further studies would be necessary to analyze the exact number of glands more suitable to be infiltrated to obtain clinically significant results.

The use of ultrasound facilitates glandular localization and guarantees the application of the drug in the right place even when there are significant anatomical alterations. Despite the fact that there are studies where the infiltration of the parotid glands is carried out by anatomical references, as these glands are considered directly accessible for injection, as in Lagalla et al. [13] or Aguilar et al. [8], we applied ultrasound-guided infiltration in both submandibular and parotid glands, thus reducing the risk of adverse effects derived from infiltration, such as facial nerve trauma. We have described only 2.98% of patients procedure-relate complications: one case was
secondary to technique injection, causing an hematoma, and 6 cases of complications derived from the toxin as saliva thickening and dysphagia. In the study by Dogu et al. [10], the use of ultrasound-guided botulinum toxin in the parotid glands was compared with anatomical references, and the study concluded in favour of the ultrasound guide. Currently, we can find guidelines that recommend the injection of botulinum toxin into the salivary glands for the treatment of hypersalivation with ultrasound guidance, as Association of Scientific Medical Societies in Germany. They describe the technique as effective and safe with long-lasting salivary reduction [14].

In general, the current scientific literature demonstrating the efficacy of botulinum toxin infiltrations in sialorrhea has done it under general anesthesia to ensure adequate localization of the toxin in the glandular tissue. However, in our center we usually carry out the infiltrations in the consultation room without sedation, using distractors that improve the child's collaboration in the procedure. When comparing the sample of patients who did require general anesthesia with those who were infiltrated in the consultation, we did not observe significant differences in the efficacy results obtained. However, this result should be contrasted with a larger study because the number of patients infiltrated under general anesthesia, in our study, is small and not comparable to infiltration group using distractors [15-19].

Conclusion

In conclusion, infiltration with ultrasound-guided botulinum toxin is an effective treatment for sialorrhea. Prospective studies are needed to analyze the selection criteria of the type of gland, the number of glands and the dosage administered, individualized according to the characteristics of the patient's sialorrhea. Thus, it would be necessary to study the use of sedation as a factor associated with improving the technique using a prospective study with a control group.

References

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