Injection of botulinum toxin type a to reduce saliva in patients with neurological diseases

Aplicação de toxina botulínica tipo A para reduzir a saliva em pacientes com doenças neurológicas

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ABSTRACT

Objective: To demonstrate the effect of local injection of Botox® in patients with neurological diseases, following our protocol for the treatment of sialorrhea. Study design: clinical prospective study. Methods: Twenty-one patients with neurological diseases seen at the Otorhinolaryngology of the Associação de Assistência à Criança Deficiente. They were all submitted to local injection of Botox® in salivary glands and followed up for one year. The protocol consists of a clinical questionnaire about inability to swallow saliva and its repercussions in general health and quality of life. Patients must not have periodontal disease or intolerance to adverse effects of anticholinergic agents and must not have used Botox® at least in the last six months. The injection was ultrasonographically guided and the dose was 30 U in one site of the submandibular glands, and 20 U in two sites in each parotid gland. Results: Twenty-one patients with sialorrhea resulting from several neurological diseases (chronic encephalopathy, Parkinson’s disease, amyotrophic lateral sclerosis, neuromuscular diseases, cerebral tumor, trauma), aged 2 to 66 years old, were submitted to Botox® injection in their salivary glands. We observed a markedly improvement of sialorrhea in all but one patient. Seventeen patients had no complaints of sialorrhea or saliva aspiration for approximately four months with good repercussion in their quality of life. No patient presented local or systemic effects with local injection of Botox®. Conclusion: the injection of Botox® as indicated in the present study was able to reduce sialorrhea resulting from several neurological conditions.

Keywords: Salivary glands; Botulinum toxin type A /therapeutic use; Sialorrhea/drug therapy; Dysphagia; Nervous system diseases

INTRODUCTION

The use of botulinum toxin to reduce saliva was first reported by Dickson & Shevky, in 1923(1), in experiments...
performed in cats. The in vivo use of botulinum toxin in salivary glands was first reported in patients with amyotrophic lateral sclerosis (ALS) to block the action in cholinergic autonomic fibers\(^2\).

In a number of neurological diseases, saliva stasis in the oral cavity, oropharynx and/or extraoral leakage of saliva indicate a neurogenic failure in coordination of tongue, palate, and facial muscles that participate in the first stage of swallowing\(^3\). About 50% of patients with ALS\(^3\), 70% with Parkinson’s disease\(^5\) and between 10 to 80% of patients with cerebral palsy\(^6\) present marked disorders of saliva control\(^3\). Additionally, hundreds of patients with neurological diseases have this abnormality. These problems increase the social stigma of the disease, leading to difficult social integration and rehabilitation and worsening of depression.

Anticholinergic drugs, antiparkinson drugs, surgical treatment of salivary ducts or glands, radiotherapy on the salivary glands and, more recently, injection of botulinum toxin type A (Botox\textsuperscript{®}) in the salivary glands are some therapeutic options. Many patients present intolerance to adverse effects of the drugs used or suffer from advanced and severe neurological diseases, making them eligible for surgical treatment; in these cases, Botox\textsuperscript{®} is the best alternative to treat sialorrhea. However, the medical literature has small and heterogeneous population samples, and doses and injection site and techniques vary much.

**OBJECTIVE**

To demonstrate the results of injection of Botox\textsuperscript{®} in a prospective study with a group of patients with sialorrhea secondary to neurological diseases of different etiologies. Standardized doses and injection techniques were used to reduce saliva and the symptoms resulting from incapacity to control saliva, as well as the repercussions in general health and quality of life.

**METHODS**

Between January 2003 and January 2005, 21 patients with sialorrhea secondary to neurological disease of different etiologies were consecutively selected at the Otorhinolaryngology Clinic of the Associação de Assistência à Criança Deficiente - AACC [Association for Assisting Handicapped Children] for injection of Botox\textsuperscript{®} in their salivary glands. Follow-up was performed 10 days after injection (first evaluation) at subsequent monthly evaluations for 12 months. The inclusion criteria used were:

1. Established neurological diagnosis;
2. Clinical manifestations suggestive of sialorrhea: accumulation of saliva in the oral cavity with continuous need of elimination, oral leakage of saliva, difficulty in speech impaired by accumulated saliva in the oral cavity and pharynx. Symptoms secondary to dysphagia or aspiration of saliva: throat clearing and hypersecretion, night waking with cough, suffocation and need to eliminate saliva;
3. Intolerance to the use of anticholinergic drugs;
4. Non-utilization of botulinum toxin in other sites in the last 6 months;
5. Dental treatment and absence of periodontal disease;

The questionnaire to evaluate the results and quality of life was answered on the day of injection (pre-injection) and in each subsequent visit (post-injection) and the answers were given as three categories (never, occasionally or frequently). The five questions covered the need to eliminate saliva from the mouth or pharynx, night waking to eliminate saliva, participation in the family group during the meals, embarrassment in public places due to sialorrhea, need to have the saliva mechanically aspirated from the upper airway digestive tract (UADT). Injection treatment and quality of life were considered successful when a minimum of three responses from the pre-injection period were changed from “frequently” to “never\textsuperscript{a}” in the post-injection period.

**INJECTION TECHNIQUE**

Topical anesthesia with prilocaine was performed in the parotid (PT) and submandibular (SM) gland areas, 30 minutes before injection. Botox\textsuperscript{®} was injected in two sites in the parotid area: 10 Units were injected in the angle between the posterior branch of the mandible and the mastoid process and 10 Units in the angle between the zygomatic process and the ascending process of the mandible (figure 1). In the SM, the injection was guided by ultrasonography (USG), and 30 U were injected in a central location in each gland (figure 2).

**RESULTS**

Between January 2003 and January 2005, 21 consecutive patients with neurological disease of different etiologies (figure 3) were submitted to injection of Botox\textsuperscript{®} to reduce saliva secretion. Age range was 2-66 years (figure 4). The most important symptoms observed in children were predominantly aspiration of saliva since they received enteral feeding and had complete restriction of oral feeding. Minimum follow-up was 12 months not taking into account the repetition of the injection. Twenty patients experienced significant improvement of symptoms and quality of life according to our success criteria and were willing to receive a new injection. One patient did not show reduction of saliva and presented the most severe...
In 17 patients, improvement extended up to the fourth month, and in three patients the action of Botox® was not present on the third month after injection.

**DISCUSSION**

Healthy individuals secrete between 1,000 and 1,500 ml of saliva in 24 hours\(^4\). Several neurological diseases evolve with deficient oral motor control. When saliva production exceeds the individual’s capacity to transport it from the mouth to the stomach, stasis, extraoral leakage and aspiration may occur in addition to concomitant difficulty chewing, articulation and speech impairment. Oral saliva leakage is stigmatizing and the prevalence is high in many neurological diseases. Sialorrhea affects about 50% of patients with ALS and 20% of them need to continuously eliminate saliva\(^3\). The prevalence of this disorder is approximately 70% in Parkinson’s disease\(^5\) and between 10%-80% in patients with cerebral palsy\(^6\). The prevalence of sialorrhea in these disorders is high and it is changes of the disease (amyotrophic lateral sclerosis), with complete immobility of the muscles in the oral cavity and oropharynx. There were no systemic or local side effects.
accompanied by social integration impairment, with marked difficulty in oral motor activities at meals and while talking, and consequent repercussions in quality of life\(^{(7)}\). Children with chronic encephalopathy (cerebral palsy), enteral feeding, and need of mechanical removal of saliva from the upper airway digestive tract (UADT) may present respiratory and pulmonary complications from chronic and persistent aspiration of saliva. In such cases, the reduction of saliva implies not only in diminishing oral leakage and easy routine care with the child but also improvement of overall health status, with a reduction in the volume of saliva aspirated into the lower airways. We selected patients with neurological diagnoses of different etiologies, which explain the wide age range in this sample. The result of saliva reduction was not different among the various neurological etiologies but it was more related with the degree of oral muscle impairment. Age did not represent a limiting factor for this treatment, and even the children (9/43\%) needed not to be sedated because the minimum restraint during identification and needle positioning by ultrasonography was already enough for the procedure. Topical anesthesia was used 30 minutes before injection. In 2004, Jongerius et al.\(^{(6)}\), reported injection under general anesthesia, when they carried out a study in which children received the injection in two regions of the SM gland, with ultrasonographic control, and accuracy would be impaired if the children were not totally immobilized.

Chronic aspiration of saliva is a risk factor for respiratory complications and it leads to abnormalities in the lung parenchyma evolving to repeated infection and chronic respiratory failure. Moreover, the need of mechanical removal of secretion from the UADT is a limiting factor for child care, including transportation and even an earlier hospital discharge of hypersecretory babies due to more intensive nursing care. Reduction of saliva may improve this impairment. In five gastrectomized children with signs of chronic aspiration of saliva, we noticed a significant improvement in all the answers to the questionnaire in addition to improvement of hypersecretion and a trend to reduce the episodes of pulmonary infection during the action of botulinum toxin.

Among the treatment options for sialorrhea, anticholinergic drugs are the most widely used to reduce saliva; however, they may have systemic side effects (urinary retention, loss of visual accommodation, headache, dry eyes), in addition to development of drug tolerance\(^{(6)}\). In patients who present seizures, spasms and irritability, which are common in children with encephalopathy, anticonvulsants may interact with this drug class; in such cases, anticholinergic drugs should be avoided or used with special caution.

Another recent option is the injection of Botox\(^{®}\) in the PT and SM glands. Although botulinum toxin has a short duration of action, and it is even discouraged by some specialists in the treatment of chronic diseases because it requires multiple injections\(^{(4)}\), in our opinion, it is a little invasive procedure, with mild or no local or systemic side effects, and it is an excellent treatment alternative.

Medical literature presents a great number of aspects in terms of technique, dose, number of injection sites in the glands, selection of salivary glands to be treated, criteria used for treatment response, and side effects. Given the small number of studies that are able to objectively clarify all these aspects, we would like to emphasize the importance of establishing a treatment protocol, with standardized injection technique and botulinum toxin dose, as well as objective quantitative and qualitative studies about saliva secretion. The action of botulinum toxin in the salivary glands takes place by inhibition of acetylcholine uptake in the neuroglandular junction; however, different from the neuromuscular action, other autonomic stimuli are responsible for saliva secretion\(^{(6)}\). Therefore, the action in the salivary glands may be individual and dependent on other non-cholinergic stimuli, and likewise, the action of botulinum toxin may also be individual and variable. We observed inefficient action with injection of Botox\(^{®}\) in only one patient; this patient evolved with rapid progression of the neurological disease.

In the review performed, the glands selected to receive Botox\(^{®}\) injections were PT alone\(^{(4)}\) or SM\(^{(6)}\) glands, a combination of injections simultaneously in the two groups (PT and SM)\(^{(4)}\), or still, injection in the PT glands and, if the desired effect was not reached within two weeks, reinjection would be performed at PT and SM\(^{(6)}\). Since PT and SM are responsible for 80%-90\% of the salivary secretion at rest, we decided to include the two groups at the same time of injection, assuming a more intense reduction of saliva would lead to better results.

In the first reports there was no description about the use of ultrasonography to guide the injection. More recent studies reported the difficulty to identify the SM gland by palpation, and they stated that the method accuracy could be increased with direct visualization of the needle under ultrasonographic control. Other authors suggested the injection should be applied in the PT gland, in one\(^{(2,7)}\), two\(^{(9)}\) or three sites\(^{(9)}\). Jongerius et al. radiologically demonstrated that the best distribution of the substance in the SM occurs with the injection in two sites\(^{(6)}\). In our practice, we observed...
that the PT gland is superficial and the anatomical landmarks are more easily identified with palpation; however, especially in children, the SM gland is more difficult to be identified and there is a risk of injecting the drug in the suprahypoid muscles, outside the SM gland, with no effect in saliva reduction. Therefore, accuracy can be attained by ultrasonography-guided injection going beyond the capsule and performing a deep injection.

According to the medical literature, the dose injected in the PT varied from $5U^{(7)}$ to $72U^{(3)}$ of Botox®, and in the SM, from $5U^{(3)}$ to $50U^{(6)}$. We established the dose of $20U$ in PT (distributed into two sites) and $30U$ in SM (in one site) glands. This was the initial dose, and when we noticed some efficacy in saliva reduction we suggested having control groups using the same technique, with dose reduction, in order to find the lowest dose leading to the same clinical result.

Another very controversial issue is report of success described in all studies, which surprisingly used different doses and techniques. This may be justified by subjective pre- and post-injection controls. In most studies, the success rate is obtained with the patient subjective response about sialorrhea control; in others, it reflects the weight of dry cotton inserted in the oral cavity before and after injection$^{(4)}$. The most objective criterion described analyzed the results of a questionnaire about quality of life and scintigraphy of the salivary glands$^{(3)}$. Our improvement criterion was a subjective evaluation with a questionnaire comprising four questions answered by patients, showing reduced extraoral leakage of saliva, reduced symptoms of dysphagia and chronic aspiration of saliva, as well as social reintegration which allows us to infer that reduction of saliva secretion and improvement in overall health status and quality of life. Twenty out of 21 patients benefited from the injection of botulinum toxin. At the end of the follow-up period, all patients expressed their wish to receive the injection again, which also reflects the treatment success. Minimum action time of Botox® with clinical responses was three months. The patient who had no successful treatment was in a very advanced stage of the underlying disease, which was also reported by other authors$^{(3)}$. All authors reported successful results with injection of Botox® in salivary glands in most patients studied.

In patients with chronic degenerative conditions, such as Parkinson’s disease, ALS and neuromuscular diseases, the marked reduction in oral leakage of saliva with the use of botulinum toxin was mentioned by many patients as the only really significant improvement observed by them and by family members since the onset of the disease. This improved the patient overall clinical status and brought hope by means of unusual therapeutic alternatives.

We did not observe any increase in the incidence of dental problems with reduction of saliva in spite of the follow-up for 12 months, although we emphasized the importance of strict dental hygiene and dental treatment prior to the drug injection, since the reduction in volume of saliva with the anticholinergic agents is related with thicker saliva. Some authors stated that the reduction of salivary flow might cause an increase in the incidence of dental decays$^{(9)}$. Among the potential adverse effects are xerostomia and worsening of dysphagia due to diffusion of the drug to the masticatory muscles. No adverse effect was found in our patients.

CONCLUSION

The injection of $20U$ of Botox® in the parotid glands and of $30U$ in the submandibular glands, by using the technique advocated in this study, was enough to decrease the secretion of saliva for four months and improve the overall health conditions and quality of life in patients with oropharyngeal dysphagia secondary to neurological diseases; moreover, it is an alternative treatment to sialorrhea.

REFERENCES

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