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Original Article

Botox injection in treatment of sialorrhea in children with cerebral palsy

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Abstract: Background: The occurrence of sialorrhea (drooling) in children with cerebral palsy is one of the important complications of this disease, which is associated with the impaired quality of life of patients and also the dissatisfaction of their parents. Botox injection in the salivary glands is one of the treatment methods that has recently received special attention in these patients, but there are still many challenges regarding its effectiveness and safety. We aimed to test the effectiveness and safety of botulinum toxin type A in reducing sialorrhea in children with cerebral palsy. Methods: This semi-experimental before-after study was performed on 12 children who suffering from sialorrhea. The ethics code of this project is IR.MUI.MED.REC.1400.774 and the clinical trial registry code is IRCT20220516054868N1 (https://www.irct.ir/trial/64393). In each of the parotid and submandibular glands, an amount of 0.5 U/kg of botulinum toxin type A was injected by ultrasound guidance under general anesthesia. Before and 6 months after the intervention, the severity and frequency of drooling were tested by Drooling Frequency and Severity Scale. Results: We found a decreasing trend in the severity and frequency scores for drooling within one month; however, after that time, until the end of the 24th week, we saw an increasing trend in the intensity and frequency of this complication. Only two-thirds of parents were satisfied with the therapeutic protocol. Side effects related to botox injection were revealed in 25.0% mostly as dysphagia. Conclusion: Botox injection in salivary glands is not a definitive and stable treatment in the treatment of sialorrhea in children with cerebral palsy.

Keywords: Botox, sialorrhea, cerebral palsy

Introduction

Cerebral palsy consists of a group of disorders identified by movement disturbances due to muscle tone defects that show abnormal control over the movement function of the central nervous system [1]. Cerebral palsy is the most common cause of disability in childhood and its incidence is increasing [2]. Sialorrhea is a common clinical sequel in children suffering from cerebral palsy with an overall prevalence of 20 to 22% [3]. Sialorrhea causes health and psychological problems in these patients, which causes stress and social isolation for the family and the patient. Children who suffer from sialorrhea may suffer from damage and dermatitis of the skin around the mouth, electrolyte disorders, and even dehydration [4, 5]. The need for frequently changing clothes reduced communication with family and friends, inflammation and infection around the mouth, and tooth decay are also other physical problems that arise for these children [6, 7].

Saliva secretion is primarily controlled by the parasympathetic system, whose postganglionic fibers enter the salivary glands directly. It is given that it can reduce saliva production and improve sialorrhea [8]. Oral sensory-motor therapies, anticholinergic drugs, surgery and intraoral devices are the methods used to improve sialorrhea in these patients, which have degrees of success and of course some potential side effects. These treatment methods are mainly favorable in mild cases of drooling and the main side effects are systemic anticholiner-

gic adverse effects and lack of compliance for intra-oral devices especially in patients with cerebral palsy [9, 10].

Botulinum toxin A (BTX-A) is one of the primary interventions in patients with sialorrhea, which was first used to reduce sialorrhea by Bushara and colleagues in 1997 through injection into the salivary glands in an adult patient with amyotrophic lateral sclerosis [11, 12]. Recently, the use of BTX-A injection has been proposed as a therapeutic alternative to reduce physical problems such as sialorrhea in children with cerebral palsy [13]. Botulinum toxin A prevents the release of acetylcholine in the synaptic space by inhibiting a protein that causes the release of vesicles containing acetylcholine in the cell membrane and thus reduces the secretion of saliva [14, 15]. In a meta-analysis study, botulinum toxin type A injection has been shown to reduce sialorrhea in many neurological diseases such as Parkinson's, amyotrophic lateral sclerosis, and cerebral palsy compared to placebo, but the dose and preparation of the toxin differed in the studies [15]. In another study, Jost and colleagues reviewed the beneficial effects of botulinum toxin type A in treatments of sialorrhea [13]. Similar results were shown by Türe and colleagues in 2021 [16]. But these studies have been conducted on restricted and small populations.

The effectiveness of using botulinum toxin type A to reduce sialorrhea in people with cerebral palsy is still unclear. The present study aimed to test the hypothesis that the use of botulinum toxin type A can effectively reduce sialorrhea in children with cerebral palsy. Due to the psycho-social and physical problems that sialorrhea causes in children with cerebral palsy, it is crucial to conduct this study and determine the effect of botulinum toxin A and the appropriate dosage to control sialorrhea in these children. By improving the quality of life and health of affected children, this study has the potential to significantly impact the care of patients with cerebral palsy.

Methods and material

Study design

This semi-experimental before-after study was performed on 12 children who suffering from sialorrhea that referred to a referral hospital in Isfahan, Iran in 2022. The ethics code of this project is IR.MUI.MED.REC.1400.774 and the clinical trial registry code is IRCT20220516054868N1 (https://www.irct.ir/trial/64393).

Inclusion and exclusion criteria

The inclusion criteria were having cerebral palsy, age of less than 16 years, having a Drooling Frequency and Severity Scale of more than 4 and signing written informed consent by the parents or the legal guardians to participate in this study. The exclusion criteria were contraindications for botulinum toxin injection from myasthenia gravis and Lambert-Eaton syndrome, Botox injection in the last three months, receiving systemic medicine for the treatment of sialorrhea in the last three months, and performing jaw and facial surgery that might interfere with the production and flow of saliva.

Drooling frequency and severity scale

This scoring system has been developed to assess semi-quantitatively the frequency and severity of drooling in patients with cerebral palsy [17]. In this scaling tool, the frequency of drooling rates as never (1 point), sometimes (not every day) (2 points), specials (every day) (3 points) and always (4 points). The severity of this event as dry (no drooling) (1 point), mild (lips only) (2 points), medium (lips and chin) (3 points), severe (clothes get wet) (4 points) and a lot (clothes and things get wet) (4 points).

Study intervention

First, 100 units of botulinum toxin type A (Botox®, Masport, Iran) was diluted with 2 ml of normal saline. The child was placed in the supine position so that the head could turn to both sides. Then, in each of the parotid and submandibular glands, an amount of 0.5 U/kg was injected by ultrasound guidance under general anesthesia. A 25G needle was used for injection. After the injection of botulinum toxin, the patient's parents were asked to evaluate the amount of drooling of the child before and after the injection using Drooling Frequency and Severity Scaling method. Parents were also asked to report any possible complications. Patients were evaluated before injection, 2 weeks, one month, 2 months, 4 months

Table 1. Baseline characteristics of study population

Variable	N (%)/ Mean ± SD
Gender, %	
Male	4 (33.3)
Female	8 (66.7)
Mean age, year	6.87±4.12
Underlying disorders, %	
Seizure	8 (66.7)
Heart failure	1 (8.3)
Laryngomalacia	1 (8.3)
Cleft palate	1 (8.3)
History of surgery, %	9 (75.0)
Number of previous hospitalization, %	
1	2 (16.7)
2	1 (8.3)
5	4 (33.3)
10	1 (8.3)
20	2 (16.7)
Causes for hospitalization, %	
Respiratory infection	4 (33.3)
Respiratory infection + repairing surgery	1 (8.3)
Respiratory infection + seizure controlling	2 (16.7)
Lower limb surgery	1 (8.3)
Tonsillectomy	1 (8.3)
Acute abdominal pain	1 (8.3)

SD: standard deviation.

and 6 months after injection. A decrease of more than 2 points on the pointed scale was considered a success of the test.

Study indicators

During the study, the following indicators were measured: 1. Demographic data, using checklists; 2. Previous surgical interventions, using medical documents; 3. Frequency of drooling, using the Drooling Frequency and Severity Scale; 4. The severity of drooling, using the Drooling Frequency and Severity Scale; 5. Complications.

Statistical analysis

For statistical analysis, results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by frequency (percentage) for categorical variables. The trend of the changes in disease severity score, the repeated measure ANOVA test was used. For the statistical analysis, the statistical software SPSS version 23.0 for Windows (IBM, Armonk, New York) was used. *P* values of ≤ 0.05 were considered statistically significant.

Results

Study population

In the current study, in total 12 patients were assessed. The average age of the participants was 6.87±4.12 years ranged 1 to 16 years and 66.7% were female. The most common underlying disorder was seizure and was found in 66.7% of patients. Also, 75.0% had a previous history of different types of surgeries such as PEG insertion, tonsillectomy, endoscopy and fundoplication due to gastric reflux, repairing of cleft palate, lower limb surgery (tibial repairing surgery), and dental restorative surgery. Overall, 58.3% of patients were hospitalized at least 5 times mostly related to respiratory infection (**Table 1**).

Drooling changes

Regarding the changes in the severity of drooling (**Figure 1**), we found a decreasing trend in the score for drooling severity within one month of intervention using Botox injection; however, after that time, until the end of the 24th week, we saw an increasing trend in the severity of this complication. Regarding the frequency of drooling (**Figure 1**), the decrease in frequency was observed only during the first 4 weeks after the intervention, and after that we faced an increase in the frequency of this complication. Overall and concerning the volume of drooling considering dryness of lips and clothes (**Figure 1**), the decrease in the severity of this event was recorded within one month of intervention with an increasing trend after that.

Complications

In total, side effects related to Botox injection were revealed in 3 patients (25.0%) and the most common complications were dysphagia in 2 patients (16.7%) and bleeding from the site of injection in 1 patient (8.3%). Concerning parents' satisfaction, only two-thirds of parents were satisfied with the therapeutic protocol, while 33.3% of them expressed being unsatis-

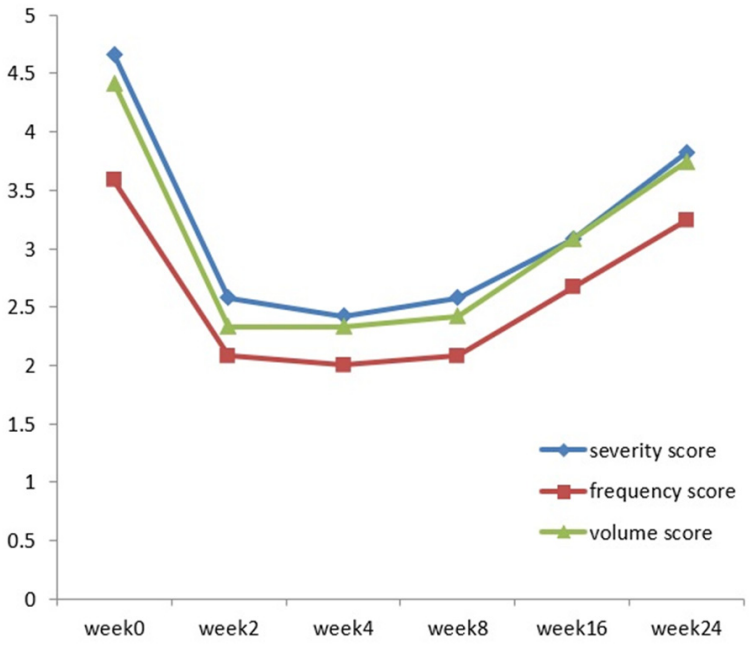

Figure 1. The trend of the changes in severity and frequency score of sialorrhea.

fied with Botox injection for controlling sialorrhea.

Discussion

Although there is evidence of the therapeutic effect of botox injection in the treatment of sialorrhea, the results of our study do not support this effectiveness. The treatment effect of this method was observed only about four weeks after the treatment intervention, and in longer-term evaluations, this treatment effect was completely neutralized.

The same finding was emphasized by the dissatisfaction of a significant part of the parents regarding the worsening of sialorrhea symptoms sometime after the start of the treatment. In other words, botox injection alone may not be a definitive treatment for sialorrhea in such patients and can only be used as a complementary treatment along with other treatments. Of course, it should be kept in mind that our study was not a randomized clinical trial study and its small sample size was considered one of its potential limitations, so the conclusion can only be reached by designing and conducting a high-powered clinical trial.

On the other hand, what dosage of the drug and for how long the treatment can have lasting therapeutic effects is still a challenge. But overall, the present semi-interventional study does not support the effectiveness of Botox injection in improving the severity of sialorrhea or its frequency.

However, a review of studies indicates the effective role of Botox injection in the treatment of sialorrhea in children, especially its chronic form, although some have still questioned this role. As indicated by Fan and colleagues in 2022 [18], botox injection in the salivary gland could result in reducing unnecessary hospitalization, usage of anticholinergics, and additional surgeries for sialorrhea management in children under 3 years of age. In a systematic review by Heikel and others in 2022 [19], by reviewing 31 studies on about 1000 patients suffering sialorrhea, the dosing of 50 units total of onabotulinumtoxinA to the submandibular glands was safe and effective in the pediatric population, while for 4-gland injections, bilateral submandibular and parotid gland injections of 60 to 100 units total were shown to be safe and effective dosage. In another study by Yu and colleagues in 2022 [14], a meta-analysis of 17 studies on 981 patients, it was shown that botox injection could relieve sialorrhea after 4 and 12 weeks of follow-up without significantly more severe adverse effects in adults, however, the certainty of the evidence was shown very low to low in children. Therefore, several hypotheses can be proposed regarding the effectiveness or futility of this method in the treatment of sialorrhea in children with cerebral palsy.

Studies have shown that Botox injections are effective in reducing drooling in children with cerebral palsy, with some reporting up to a 90% reduction in drooling [20]. The effects typically last for several months and can be repeated as needed. While Botox injections are generally considered safe, they can cause side effects such as dry mouth, difficulty swallowing, and speech difficulties. There is also a risk of botulism, a serious condition that can cause muscle

weakness and respiratory problems. Therefore, Botox injections should only be performed by trained healthcare professionals with experience in administering the treatment. The decision to use Botox should also be made on a case-by-case basis, considering the child's medical history, the severity of sialorrhea, and potential risks and benefits.

First, perhaps the main effectiveness of this treatment is related to the treatment of sialorrhea in adults and also in the treatment of its chronic type, so it may not be very effective in young people. Secondly, studies have mainly considered a short-term follow-up of patients, and therefore, in the long term, we may be facing the ineffectiveness of Botox injections in the treatment of sialorrhea. Confirmation or rejection of each of these hypotheses requires conducting more clinical trials on children with sialorrhea in the field of cerebral palsy.

The main limitation of this study was the restricted study population. This issue is mainly because that parents might not consent to experimental studies on patients with cerebral palsy. Another limitation was the lack of a control group in this study, which could be due to the restricted study population. It is expected that future studies should consider larger populations and different doses of Botox for treatments of sialorrhea.

Conclusion

It can be finally concluded that the use of botox injection in children with cerebral palsy with sialorrhea has limited and short-term therapeutic effects and does not satisfy the parents. Therefore, this treatment method cannot be used to reduce the severity and frequency of sialorrhea, and it can only be used as an auxiliary method along with other definitive treatment methods.

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Disclosure of conflict of interest

None.

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