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The Effects of Botulinum Toxin Type A on Reducing Sialorrhea in Children with Cerebral Palsy: A Self-Controlled Clinical Trial

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Abstract

Background: Cerebral palsy stands as the main cause of mobility disability in childhood, and the accompanying sialorrhea exacerbates health and psychological issues for both the child and the family. We aimed to assess the effect of botulinum toxin type A on reducing sialorrhea in children with cerebral palsy.

Methods: This self-controlled clinical trial was executed among children afflicted with cerebral palsy. The Teacher Drooling Scale was used as the data collection tool. The intervention involved the administration of botulinum toxin A, with a dosage ranging from 30 to 50 units in each parotid gland, skillfully guided by a radiologist using ultrasound. Sialorrhea scores were compared before and after the injection.

Results: Our study included 21 children with cerebral palsy and sialorrhea. After the two post-injection weeks, a noteworthy drop was observed in the sialorrhea score (4.10±0.831) compared to the pre-injection score (4.71±0.463). The sialorrhea score until the ninth month after injection (1.121±3.43) was still significantly lower than the score before injection.

Conclusion: The injection of botulinum toxin A emerges as a potent medication, significantly curtailing the drooling among patients with cerebral palsy. This finding can be used to prevent aspiration pneumonia and reduce social and psychological complications in this population.

Key Words: Botulinum Toxins Type A, Cerebral Palsy, Sialorrhea.

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1- INTRODUCTION

Cerebral palsy encompasses a set of non-progressive developmental-motor disorders in the developing fetus or infant's brain. Often accompanied by seizures, this condition manifests with abnormalities in speech, vision, intelligence, cognition, and behavior (1). The origin of cerebral palsy is the central nervous system, and this condition causes disturbance in the movement and posture of body organs, which have a static state (2). While the incidence of cerebral palsy in term babies remains steady despite perinatology advancements, there is a rise in premature births, attributed to enhanced survival rates owing to technological progress. The incidence stands at 2 to 3 per thousand live births and 40 to 100 per 1000 premature births (3).

Drooling, or sialorrhea, emerges as a prevalent issue in cerebral palsy, marked by excessive saliva secretion and involuntary oral content loss. The parasympathetic system primarily governs saliva production, with postganglionic fibers directly influencing salivary glands. Studies indicate that reducing saliva production can ameliorate sialorrhea (5-7). Various approaches, including oral sensory-motor therapies, anticholinergic drugs, surgery, and intraoral devices, are employed to address sialorrhea in cerebral palsy patients. However, these methods come with varying degrees of success and potential side effects (8).

Botulinum toxin, a product of anaerobic Clostridium botulinum, impedes the release of acetylcholine from presynaptic neurons at the nerve-muscle junction. The toxin establishes an irreversible bond with receptors at the presynaptic junction, a process taking place within 34-64 minutes in vitro. Upon binding, botulinum toxin infiltrates the cell, disrupting the essential protein for acetylcholine release in the cytosol and impedes its subsequent release. This binding occurs at the nerve terminals' end, resulting in a permanent inhibition and connection. Only with the regeneration of the axonal bud, responsible for acetylcholine release, does the nerve fiber's function return to its initial state, a process spanning 2-3 months (9). In a meta-analysis study, the injection of botulinum toxin A, compared to a placebo, demonstrated efficacy in reducing sialorrhea across various neurological diseases such as Parkinson's and cerebral palsy. However, differences in toxin dosage and preparation were noted (10). Evaluating the impact of low, medium, and high doses on sialorrhea in children with cerebral palsy revealed that a 3000MU injection of botulinum toxin B significantly diminished both the intensity and frequency of sialorrhea. Doses below this threshold exhibited no therapeutic effect, while higher doses showed no significant difference in therapeutic response but elevated side effects (11-12). Despite the acknowledged use of botulinum toxin in managing sialorrhea in cerebral palsy children, it remains imperative to ascertain the appropriate dosage, onset, and stability of effects, and the suitable target population (9). Consequently, this study was undertaken to assess the effect of botulinum toxin type A on reducing sialorrhea in patients with cerebral palsy.

2- MATERIALS AND METHODS

2-1. Design

This self-controlled clinical trial was conducted on 21 children with cerebral palsy, in 2022 at the Fayaz Bakhsh Center in Mashhad, Iran.

2-2. Sampling

Sampling was done by a convenient method among the patients. The sample size was determined based on the parameters outlined in the study by Rodwell et al., with mean scores before (M=9, SD=1.82) and after intervention (M=5.85, SD= 2.59) taken into account,

while considering α=0.05, and B= 0.2 (13, 14).

2-3. Inclusion and exclusion criteria

Inclusion criteria comprised a diagnosis of cerebral palsy, a drooling score equal to or exceeding 4, age ranging from 4 to 16 years, parental or legal guardian consent for study participation, absence of contraindications for botulinum toxin A injection (such as Myasthenia gravis and Eaton-Lambert syndrome), no botulinum toxin A injection in the preceding 4 months, and no systemic medication for sialorrhea in the past three months. Exclusion criteria encompassed evidence indicating the recent necessity for jaw and facial surgery, potentially impacting saliva production and flow, and parental non-consent for continued study participation.

2-4. Instrumentation

The instruments employed for data collection included a sample selection form, a demographic form, and the Teacher Drooling Scale tool. The Teacher Drooling Scale tool stands as a standardized measure for gauging the intensity and frequency of drooling (15). To validate the tool, a content validity assessment was conducted by seven experts in pediatric neurology and pediatric medicine. Additionally, the tool's reliability was assessed through the observer reliability (interrater) method, yielding a Kappa coefficient of 0.93.

2-5. Procedure

The intervention in this study involved administering botulinum toxin A® (MASPORT), a product manufactured in Iran. The dosage, tailored to the patient's weight, ranged from 30 to 50 units per gland (30 units for less than 15 kg, 40 units for 15-25 kg, and 50 units for over 25 kg), with injections targeted at both parotid glands.

To prepare the injection, a vial of botulinum toxin A® (MASPORT) from Iran was diluted with 3.2 cc of normal saline (9). An otolaryngologist, guided by ultrasound, conducted the injection. Caregivers/parents were informed about potential complications, including muscle weakness, double vision, speech and swallowing disorders, and urinary incontinence. Throughout the study, close monitoring of the children took place to detect any occurrence of these complications.

The severity and frequency of drooling were assessed using the Teacher Drooling Scale tool before injection and at intervals of 2 weeks, one month, 2 months, 4 months, 6 months, and 9 months post-injection.

2-6. Data analysis

Data were reported by mean, standard deviation, number, and frequency in SPSS, Version 26.0. Armonk, NY: IBM Corp. Qualitative data were analyzed by the McNemar test. The normality distribution of quantitative data was assessed by the Shapiro-Wilk test. The Wilcoxon Signed Ranks Test was used to compare quantitative variables. A P-value< 0.05 indicates statistical significance.

3- RESULTS

In this study, 21 children with a mean age of 9.38 (3.26) years and weight of (18.03 (7.96) kilograms were assessed including 11 (52.4%) boys and 10 (47.6%) girls.

As **Table 1** shows, there was a significant difference in terms of drooling score before intervention and in different time points after intervention (P< 0.05).

The frequency of outpatient treatments with antibiotics and hospitalization due to aspiration pneumonia in the same period of the previous year and in the follow-up period after botulinum toxin A injection are given in **Table 2**. The number of outpatient treatments less than or equal to

two times in the follow-up period after injection was significantly different from the same period last year (p<0.002), however, no significant difference was indicated regarding hospitalization.

Table-1: Comparing the Drooling score before and after botulinum toxin A injection

Drooling score	Mean (SD)	P-value
Before intervention	4.71 (0.46)	-
Day 15	4.10(0.83)	Z=-2.81* P=0.005
One month after	3.48 (1.07)	Z=-3.223* P=0.001
Two months after	3.29 (1.10)	Z=-3.381* P=0.001
Four months after	3.14 (1.15)	Z=-3.479* P=0.001
Six months after	3.24 (1.17)	Z=-3.461* P=0.001
Nine months after	3.43 (1.12)	Z=-3.331* P=0.001

* Wilcoxon Signed Ranks Test

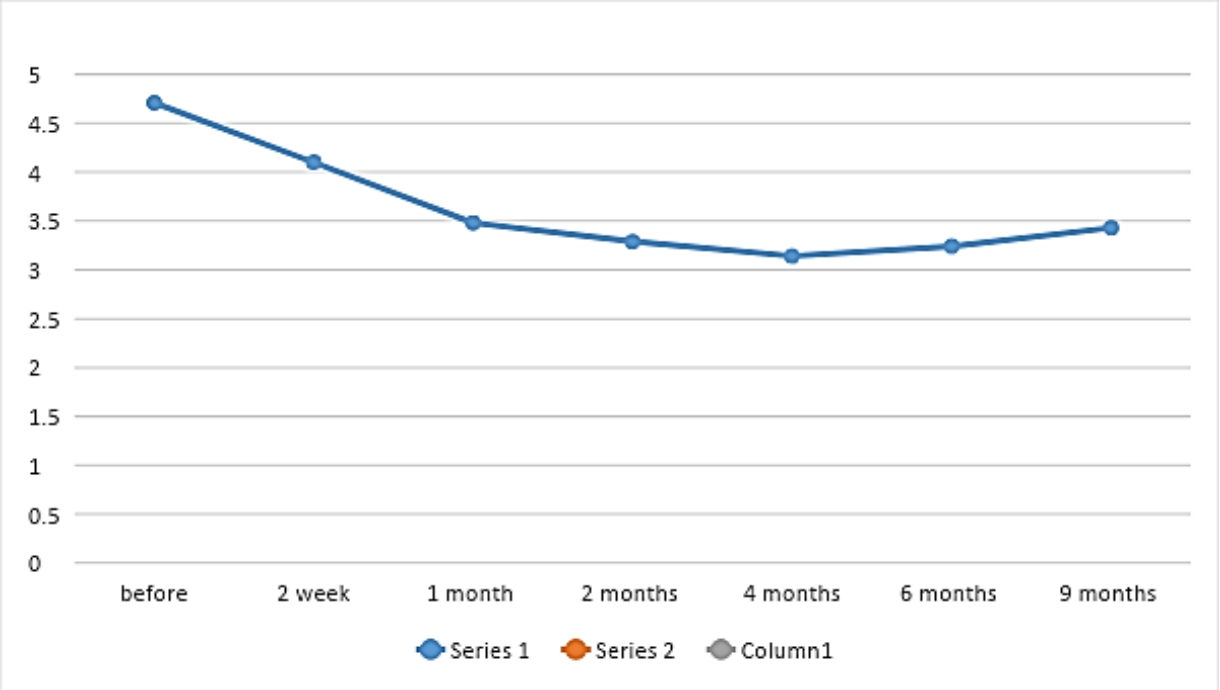

Fig. 1: Changes in the mean score of sialorrhea during the study period

Table-2: Outpatient treatment with antibiotics for aspiration pneumonia in the same period of the previous year and the follow-up period after botulinum toxin A injection

Aspiration pneumonia	the same period of the previous year num (%)	Follow-up period after botulinum toxin An injection. num (%)	p-value*
Outpatient treatment of ≥2 antibiotics	(61.9)13	3 (14.3)	0.002
Outpatient antibiotic treatment <2	38.1))8	18 (85.7)	
≥2 hospitalization	3 (14.3)	2 (9.5)	0.99
<2 hospitalization	18 (85.7)	19 (90.5)	

4- DISCUSSION

Cerebral palsy manifests as a disorder impacting posture, movement, and muscle tone. In our study, we observed a significant reduction in sialorrhea scores in children with cerebral palsy two weeks post-botulinum toxin injection, persisting until the fourth month. Subsequently, a gradual increase occurred from the sixth month, but even by the ninth-month post-injection, sialorrhea scores remained notably lower than pre-intervention levels.

Similar to our findings, Jongerius et al. administered a single dose of botulinum toxin into the bilateral submandibular glands, guided by ultrasound, in three children with severe drooling cerebral palsy. The subsequent four-month observation period revealed a satisfactory outcome, with a total of 40 to 50 botox units administered based on body weight. Quantitative sialometry, employing the weight of cotton rolls and a parental questionnaire, indicated a substantial decrease in maximum salivary secretion ranging from 51 to 63%. No adverse complications were reported during the follow-up period (16). Additionally, Bothwell et al. injected botulinum toxin into the parotid glands at a dosage of 5 units per gland. Over a 2-4-month period, they documented a notable reduction of 55% in drooling within a sample of 9 children aged 14 to 17 years old (17).

In another investigation by Ellies et al., they administered 50 to 65 units of botulinum toxin A into the parotid and submandibular glands on both sides, guided by ultrasound, in 5 children experiencing heightened salivary secretions due to neurological lesions. All injections were carried out without local anesthesia and were well tolerated. Saliva flow was assessed before injection and at weeks 1, 2, 4, and 12 post-injection, concurrently examining potential side effects. Their results indicated a parental report of decreased secretions within 2 weeks (18). These outcomes align with our study, affirming the observed clinical improvements within two weeks post-injection. However, their study demonstrated the stability of the effects up to 4 months, whereas our study revealed a sustained and significant decrease in sialorrhea scores up to 9 months after injection.

Numerous studies substantiate the favorable impact of botulinum toxin on sialorrhea in children with neurological disabilities. Botulinum toxin operates by presynaptically inhibiting the release of acetylcholine in the parasympathetic (and sympathetic cholinergic) ganglia. This effect, akin to motor terminal axon

involvement, undergoes restoration through reinnervation following terminal axon degeneration (19). According to past sources, this process takes 3 to 4 months. Notably, injecting botulinum toxin into major salivary glands has been theorized to induce a blockade of neurogenic (parasympathetic) control over salivary secretion, purported to endure for a quarter of a year (18). However, our present study reveals a remarkable stability of this effect lasting until the ninth-month post-intra-glandular injection. Notably, no prior study has either confirmed or refuted this finding (19), with the precise clinical termination time and return of secretions to baseline remaining unreported.

Yet, certain findings from the study affirm the aforementioned outcomes. Over the nine-month observation period, a significant decrease in outpatient antibiotic prescriptions for treating aspiration pneumonia was noted compared to the corresponding period in the previous year. Given that sialorrhea is recognized as a risk factor for aspiration pneumonia, the reduction in sialorrhea appears to correlate with a notable decline in antibiotic consumption.

However, it is crucial to acknowledge that the number of hospitalizations attributed to aspiration pneumonia did not exhibit a significant difference compared to the same period in the preceding year. This finding suggests that while sialorrhea contributes to pneumonia occurrence, it is not the sole factor, and its impact primarily manifests in reducing antibiotic use for mild pneumonia and outpatient treatment.

5- CONCLUSION

Our study revealed that botulinum toxin A induces a significant reduction in saliva secretion. This effect initiates in the second-week post-injection and persists until the fourth month. From the sixth month onwards, a slight increase in the sialorrhea score is noted. However, up to the ninth-month post-injection, the sialorrhea score remains significantly lower than pre-injection levels. It is noteworthy that botulinum toxin A operates by impeding the release of acetylcholine in the synaptic space, consequently diminishing saliva secretion. While the positive impact of botulinum toxin A on sialorrhea is acknowledged, future studies are essential to establish a cut-off time for botulinum toxin injection in reducing sialorrhea. Many studies have assumed a clinical effect duration of 3 to 4 months without investigating longer follow-up periods. In the current study, no specific time cut-off was determined, affirming the sustained clinical results up to ninth months after injection.

6- ETHICAL CONSIDERATIONS

This study followed the ethical principles of Helsinki and was approved by the ethics committee of Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1400.535). Also, it was registered in the Iranian clinical trials registration system (IRCT20220211053995N1). Written informed consent was obtained from the parents or legal guardians of all participants.

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