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Ultrasound-guided botulinum toxin injections of salivary glands in cerebral palsy children with sialorrhea

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ABSTRACT

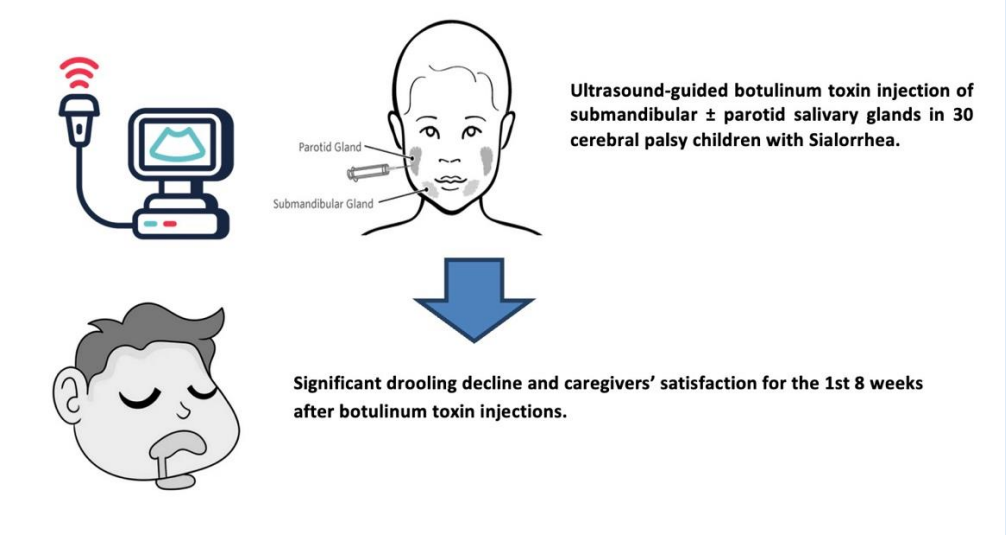
Objective: Excessive salivation and drooling are distressing problems that affect both children and their families. Salivary gland botulinum toxin injection is a widely studied therapeutic method for treating sialorrhea. The proper protocol for such treatment modality is an area of interest for researchers. This study set out to assess the success of ultrasound-guided botulinum toxin injections in either the submandibular or combined with parotid salivary glands for children with cerebral palsy suffering from sialorrhea, while also identifying factors that predict a positive treatment outcome.

Method: This cross-sectional study included 30 children with cerebral palsy who have Sialorrhea. Ultrasound-guided botulinum toxin injections of submandibular salivary glands alone or combined with parotid glands were done. Drooling was evaluated using Drooling Rating Scale, Drooling Impact Scale, and 5-minute Drooling Quotient. Children were followed up weekly for 12 weeks after botulinum toxin injections.

Result: All children showed a significant decline in drooling and sufficient caregivers' satisfaction for the first 8 weeks after botulinum toxin injections, with gradual worsening of drooling later in 60% of children. Assessment scores were significantly lower in those who received combined parotid and submandibular injections than those who received submandibular gland injections alone. Changes in drooling scores have a significant negative correlation with the severity of motor disabilities.

Conclusion: Submandibular salivary gland injection alone has a satisfactory response in decreasing drooling in children with cerebral palsy. However, a combined injection of both parotid and submandibular salivary glands gives a better response for at least 8 weeks without complications. This study not only addresses the clinical effectiveness of botulinum toxin injections in managing sialorrhea in children with cerebral palsy but also opens avenues for improved dietary strategies.

Keywords: botulinum toxin; salivary gland; sialorrhea; cerebral palsy



INTRODUCTION

Salivary drooling or sialorrhoea is a common comorbidity in children with neurological disabilities. About 40% of children with cerebral palsy suffer from drooling; one in three patients has significant drooling that needs intervention [1]. Children with cerebral palsy are vulnerable to drooling due to their mental and physical disabilities, oral motor dysfunction, and uncoordinated lip movement, causing dental malocclusion and open bite. Drooling negatively affects the quality of life, causing great embarrassment and social withdrawal for both affected children and their caregivers. Continuously drooled saliva causes skin irritation, wetting of clothes and surrounding machines. Furthermore, it interferes with feeding, swallowing, and speech causing local oral and dental inflammation [2].

Drooling occurs continuously and is not limited to meals. It is usually categorized into anterior drooling along the lip margin or posterior drooling, causing recurrent choking and aspiration. Children with cerebral palsy may develop anterior, posterior, or both, which have been reported in 26% to over 70% of individuals with cerebral palsy [3]. Drooling may be primarily caused by increased saliva production due to teething or oral mucosa irritation. Secondary sialorrhea is usually caused by insufficient drainage of saliva from the mouth, which represents the main cause of drooling in children with cerebral palsy [4].

Submandibular salivary glands secrete semi-viscous saliva, accounting for the majority (70%) of un-stimulated whole saliva and 25% of saliva secretion when oral mucosa is stimulated. Parotid gland secretion is watery saliva that occurs mainly (70%) during oral mucosal stimulation and mastication and 25% in un-stimulated status. The total amount of un-stimulated saliva in

healthy children aged 6–11 years old ranges between 0.14–1.30 mL/minute [5].

Several interventional strategies have been tried to control drooling in children with neurodevelopmental disabilities, including surgery, medications, physiotherapy, behavioral therapy, and botulinum toxin injection into salivary glands [6,7].

Intra-glandular botulinum toxin injection blocks the release of acetylcholine into the neuromuscular synapse, leading to transient local salivary gland denervation without causing a systemic anticholinergic effect. Synaptic transmission block induced by botulinum toxin injection represents an effective, less invasive alternative to surgical interventions. However, the required doses, the number of glands to be injected, and the maximum duration of action are still controversial [8].

The location of the salivary glands varies based on the children age and body weight. The parotid gland position is superficial, while the submandibular gland is deep and difficult to locate by palpation. Ultrasound accurately determines the salivary glands' location, depth, and blood supply. In addition, ultrasound-guided injection provides a safe and accurate tool to deliver the medication into the gland without infiltration into the surrounding muscles and tissues [9].

Botulinum injection into the submandibular glands alone has been reported to be effective in reducing drooling [10]. The present study aimed to evaluate the efficacy of ultrasound-guided botulinum toxin injections of submandibular salivary glands alone or in combination with parotid glands in cerebral palsy children with sialorrhea and assess predictive factors for good response.

PATIENTS AND METHODS

Study Population: In this study, we looked at 30 kids with cerebral palsy who had issues with drooling. Their caregivers were on board and stuck with us for a 12-week follow-up. We selected these kids from the neurology and pediatric clinics of Alzahraa University Hospital. Everything was above board, with the ethics committee at the Faculty of Medicine for Girls, Al-Azhar University giving us the approval (IRB number 202001033). We made sure the parents were clued in about what we were doing and got their written consent. The kids got ultrasound-guided botulinum toxin injections right in their submandibular salivary glands, alone or combined with the parotid glands too. Over 12 weeks, we checked in on them every week. The physcians doing the follow-ups didn't know the type of saliva control intervension, keeping it a fair test. The included children were randomly divided into 2 groups. Groups were randomized by number (odd numbers were included in Group 1, and even numbers were included in Group 2). Group 1 (include odd-number children): 15 children who were injected into submandibular salivary glands alone. Group 2 (include even-number children): 15 children were injected into submandibular salivary glands in combination with parotid glands.

To be included in the study, we looked for children between the ages of 4 and 10 years who had cerebral palsy and sialorrhea. We made sure to exclude children with chronic upper airway obstructions, like those caused by structural issues, orofacial deformities, dental problems, or other neuromuscular diseases. We also excluded children who had already received treatment for drooling. Cerebral palsy was defined as neurological motor disability due to non-progressive insult affecting the developing brain. According to the pattern of motor affection, it was categorized into the spastic, dyskinetic, and mixed pattern; the spastic type was further classified according to the involved limbs into quadriplegic, diplegic, and hemiplegic [11].

Methods: All studied children were subjected to: Full history taking with stress on neurological symptoms, the age of onset, perinatal and developmental history, drooling frequency, severity, the impact of drooling on the child and family, feeding, swallowing problems, and aspiration.

Thorough physical examination including Detailed general and systemic examination with stress on craniofacial malformations, dental and neurological examination. Anthropometric measures: weight, length, body mass index. All parameters were expressed as z-scores according to World Health Organization charts for age and sex. Otorhinolaryngology examination assesses airway and nasopharynx patency by reviewing lateral nasopharyngeal x-rays and excluding those with chronic upper airway obstruction to eliminate confounders that may increase drooling. The Gross Motor Function Classification System (GMFCS) for cerebral palsy was used to categorize the severity of motor disability into 1 to 5 grades [12].

Assessment of drooling was done using: (1) Drooling Rating Scale for severity and frequency: it is a subjective tool that is widely used to assess the severity and frequency of drooling in children with neurological disabilities. It consists of 5 items for the severity with a score 1 to 5 and 4 items for the frequency that scored 1 to 4 [13]. (2) Drooling impact scale (DIS): it is a subjective assessment tool that identifies longitudinal changes in drooling in response to medical intervention. It consists of 10 items that were scored on a 10-point scale. It is based on assessing the impact of drooling on both children and their caregivers and evaluates their satisfaction with the response to management interventions [14]. 3- 5-minute Drooling Quotient (DQ-5): It is a standardized observation of drooling every 15 seconds for 5 minutes during the performance of an activity (playing with a toy) and another 5 minutes during rest (watching a screen). The observation was done under standardized conditions in a sitting position one hour after mealtime with the mouth empty and clean before starting the observation and saliva wiped off the chin. When we talk about drooling, we mean when saliva drips from the lower lip, mouth, or chin area, or when there's a noticeable string of saliva that gets thicker and longer. The patient scored one if new saliva was formed and zero if none was formed During each 5 minutes observation, the presence (score 1) or absence (score 0) of new saliva drooling was determined at 15-second intervals (total of 20 intervals). DQ-5 was calculated as the total amount of intervals with new saliva multiplied by 100 and then divided by the total number of intervals (=20). Clinical response was defined as a ≥50% reduction in the DQ-5 [15].

Expert ENT consultant performed ultrasound-guided botulinum toxin injections on the submandibular and parotid glands. The same radiologist detected the glands and their ducts using ultrasound. The children were sedated with oral chloral hydrate, and the skin was disinfected. The injections were done under ultrasound guidance using a 25-gauge 3.8 cm needle. We used a Phillips Affinity 70G machine and a high-frequency linear transducer. After injection, the gland was gently massaged to help the botulinum toxin spread. None of the included children had developed any complications. Parents were instructed regarding oral and dental hygiene, keeping a patent upper airway by clearing the nose and proper neck posture, and avoiding tilting the head forward to decrease drooling.

Statistical analysis: Data was statistically analyzed using a statistical package for social sciences (SPSS) version 22 (IBM, USA). Numerical data was expressed as mean and standard deviation. Categorical data was expressed as frequencies and percentages. Groups were compared using students' t-tests, Mann–Whitney U, chi-square, and one way ANOVA tests [16]. Further analysis between groups was done by post hoc LSD test. Correlation between variables was detected using the Pearson correlation test. $P < 0.05$ was considered statistically significant.

Table 1. Comparison of clinical and drooling assessment scores between children injected into submandibular and those injected into parotid and submandibular salivary glands.

	2 Submandibular only (n=15)	2 Parotid and 2 submandibular (n=15)	Independent T test/ Mann–Whitney U test / chi square test	
	Mean ± SD	Mean ± SD	t/X^2	p-value
Age (years)	7.333±1.708	7.233±2.145	0.141	0.889
Male sex (N, %)	9 (60%)	10 (66.7%)	0.144	0.705
Type of CP (N, %) **Spastic** **Dyskinetic** **Mixed**	 8 (53.3%) 4 (26.7%) 3 (20%)	 10 (66.7%) 2 (13.3%) 3 (20%)	0.889	0.641
Spasticity distribution **Hemiplegic** **Diplegic** **Quadriplegic**	 2 (13.3%) 1 (6.6% 5 (33.3%)	 2 (13.3%) 3 (20%) 5 (33.3%)	0.788	0.675
GMFS (N, %) **Grade 3** **Grade 4** **Grade 5**	 2 (13.3%) 5 (33.3%) 8 (53.3%)	 4 (26.7%) 7 (46.6%) 4 (26.7%)	2.333	0.311
Epilepsy (N, %)	8 (53.3%)	9 (60%)	0.136	0.713
Intellectual disability **Moderate** **Sever** **Profound**	 2 (13.3%) 8 (53.3%) 5 (33.3%)	 3 (20%) 5 (33.3%) 7 (46.6%)	1.226	0.542
Weight (kg)	14.700±1.791	14.067±2.705	0.756	0.457
Height (cm)	104.133±7.736	103.267±9.145	0.280	0.781
DQ-5 score baseline	42.000±5.568	39.467±4.897	1.323	0.197
DQ-5 score at 1wk	23.533±7.492	13.933±3.770	4.433	<0.0001*
DQ-5 score at 8wk	26.400±8.559	15.067±4.743	4.486	<0.0001*
DQ-5 score at 12wk	34.000±7.847	29.000±4.870	2.097	0.047*
DQ5>50% decline (N, %)	8 (53.3%)	14 (93.4%)	6.136	0.013*
DIS score baseline	60.000±7.031	59.867±6.781	2.683	0.958
DIS score at 1wk	38.467±12.794	28.200±11.827	0.053	0.030*
DIS score at 8wk	41.933±13.301	31.067±11.967	2.282	0.026*
DIS score at 12wk	54.600±8.773	44.133±10.013	2.352	0.005*
Severity score baseline	4.333±0.817	4.200±0.775	3.045	0.650
Severity score at 1wk	2.000±0.926	1.333±0.488	0.459	0.022*
Severity score at 8wk	2.000±0.926	1.333±0.488	2.467	0.022*
Severity score at 12wk	3.000±1.069	2.600±0.910	2.467	0.280
Frequency score baseline	3.800±0.414	3.733±0.458	1.103	0.679
Frequency score at 1wk	2.267±0.704	1.467±0.743	0.418	0.005*
Frequency score at 8wk	2.200±0.775	1.533±0.743	3.027	0.023*
Frequency score at 12wk	2.933±0.884	2.467±0.834	2.405	0.148

*Significant. CP: cerebral palsy; GMFS: gross motor function system classification; DIS: Drooling impact scale; DQ-5: 5-minute Drooling Quotient.

RESULTS

We enrolled thirty children with cerebral palsy, consisting of 19 boys (63.3%) and 11 girls (36.7%), aged 4 to 10 years. The causes of cerebral palsy among them included 9 cases of post-anoxic origin, 4 from congenital cytomegalovirus infections, 6 following meningoencephalitis, 6 associated with kernicterus, and 3 linked to intracranial hemorrhage. When comparing the clinical and drooling assessment scores, we observed significant improvement in all scores for children who received botulinum toxin injections in both the parotid and submandibular salivary glands (4 glands) compared to those who were injected in the submandibular glands alone (2 glands). This is shown in Table 1. During the 12-week follow-up, we saw a notable drop in salivary assessment scores for both groups just one week after the injections. No significant changes were detected in the 8th week of follow-up. There was a significant increase in salivary assessment scores in the 12th week, but scores are still significantly lower than their baseline before injection, as demonstrated in Table 2 and Figure 1.

There is a significant positive correlation between salivary assessment scores and GMFS classification for cerebral palsy, as demonstrated in Table 3.

The association between clinical variables and drooling response to injection among the studied children showed significantly higher scores in those with spastic quadriplegia, grade 5 GMFS, and moderate to profound intellectual disability, as demonstrated in Table 4.

Table 2. Comparison of drooling assessment scores changes during the follow-up period.

		Baseline	At 1st week	At 8th week	At 12th weeks
DQ-5 score	submandibular	42.000±5.568	23.533±7.492	26.400±8.559	34.000±7.847
	both glands	42.467±4.897	13.933±3.770	15.067±4.743	29.000±4.870
DIS score	submandibular	60.000±7.031	38.467±12.794	41.933±13.301	54.600±8.773
	both glands	59.867±6.781	28.200±11.827	31.067±11.967	44.133±10.013
Severity score	submandibular	4.333±0.817	2.000±0.926	2.000±0.926	3.000±1.069
	both glands	4.320±0.775	1.333±0.488	1.333±0.488	2.600±0.910
Frequency score	submandibular	3.800±0.414	2.267±0.704	2.200±0.775	2.933±0.884
	both glands	3.833±0.458	1.467±0.743	1.533±0.743	2.467±0.834

Post hoc LCD test					
		Baseline vs at 1 wk.	**At 1wk vs at 8 wks.**	**At 8 wk vs at 12 wks.**	**Baseline vs at 12 wks.**
Submandibular	DQ-5 score	<0.0001*	0.296	0.007*	0.005*
	DIS score	<0.0001*	0.383	0.002*	0.177
	Severity	<0.0001*	1.000	0.005*	<0.0001*
	Frequency	<0.0001*	0.800	0.007*	0.002*
2 glands	DQ-5 score	<0.0001*	0.502	<0.0001*	<0.0001*
	DIS score	<0.0001*	0.452	0.001*	<0.0001*
	Severity	<0.0001*	1.000	<0.0001*	<0.0001*
	Frequency	<0.0001*	0.798	0.001*	<0.0001*

*Significant. DIS: Drooling impact scale; DQ-5: 5-minute Drooling Quotient.

Table 3. correlation between gross motor function system classification with salivary assessment scales before and after injection

	GMFS	
	r	p-value
DQ-5 score baseline	0.781	<0.0001*
DQ-5 score at 1wk	0.695	<0.0001*
DIS score baseline	0.817	<0.0001*
DIS score at 1wk	0.780	<0.0001*
Severity score baseline	0.889	<0.0001*
Severity score at 1wk	0.791	<0.0001*
Frequency score baseline	0.674	<0.0001*
Frequency score at 1wk	0.653	<0.0001*

*Significant. GMFS: gross motor function system classification; DIS: Drooling impact scale; DQ-5: 5-minute Drooling Quotient.

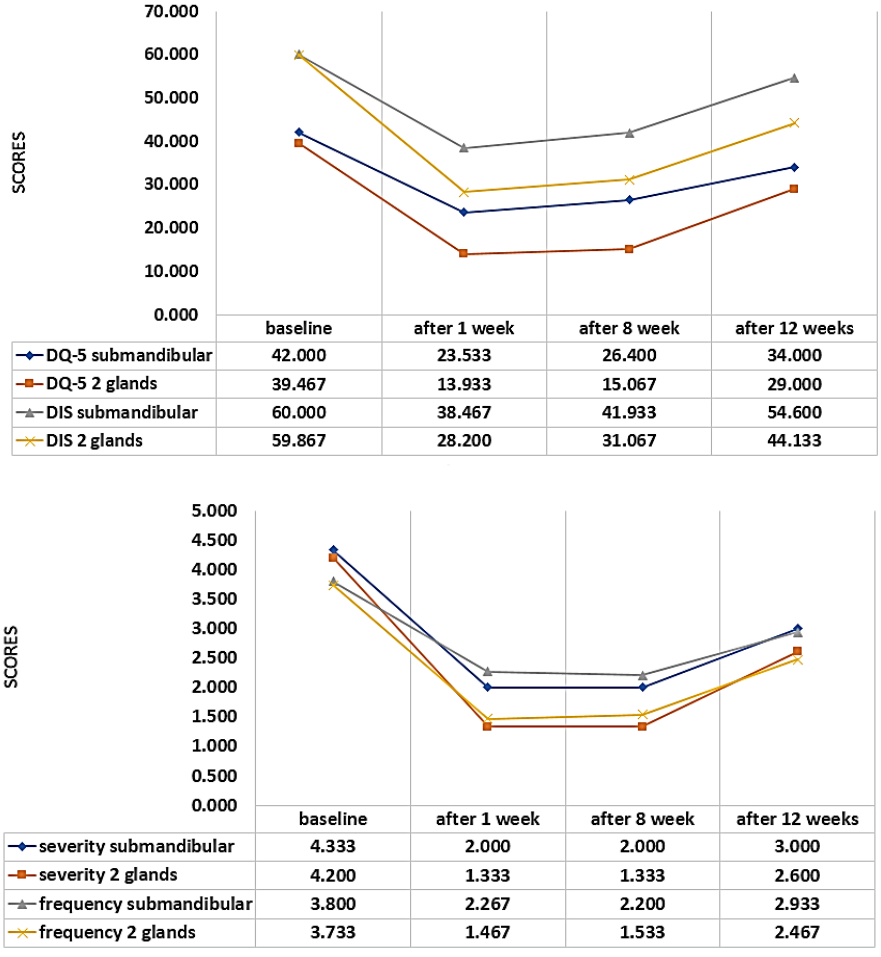


Figure 1. follow up of salivary assessment scores over 12 weeks.

Table 4. the association between clinical variables and drooling response to injection among the studied children

	Type of CP			Independent T-test/ Mann–Whitney U test/ chi square test	
	Spastic (n=18)	Dyskinetic (n=6)	Mixed (n=6)	t/x^2	p-value
DQ-5 score baseline	41.000±5.871	40.500±4.461	40.167±5.076	0.059	0.943
DQ-5 score at 1wk	18.333±7.004	19.667±8.164	19.000±10.000	0.069	0.933
DQ5≥50% decline	15 (83.3%)	4 (66.7%)	3 (50%)	2.727	0.256
DIS score baseline	59.388±7.889	61.333±3.265	60.167±6.431	0.178	0.838
DIS score at 1wk	31.333±12.797	37.500±13.307±	35.167±15.328	0.547	0.585
DIS ≥50% decline	10 (55.5%)	2 (33.3%)	3 (50%)	0.889	0.641
Distribution of spasticity					
	hemiplegic (n=4)	diplegic (n=4)	quadriplegic (n=10)	t	p-value
DQ-5 score baseline	35.250±2.061	35.250±2.500	45.600±2.951	32.491	<0.0001*
DQ-5 score at 1wk	13.250±2.753	13.250±1.707	22.400±6.915	6.042	0.012*
DQ5≥50% decline	4 (100%)	4 (100%)	7 (70%)	2.880	0.237
DIS score baseline	52.000±4.690	53.000±1.825	64.900±5.743	13.785	<0.0001*
DIS score at 1wk	22.000±6.055	20.250±4.787	39.500±11.047	8.848	0.003*
DIS ≥50% decline	3 (75%)	3 (75%)	7 (70%)	2.205	0.332
GMFS classification					
	3 (n=6)	4 (n=12)	5 (n=12)	t	p-value
DQ-5 score baseline	34.333±0.816	39.500±3.872	45.166±3.688	21.221	<0.0001*
DQ-5 score at 1wk	12.500±2.588	15.250±3.545	25.333±7.401	15.715	<0.0001*
DQ5≥50% decline	6 (100%)	12 (100%)	4 (33.3%)	16.364	<0.0001*
DIS score baseline	51.166±2.136	58.500±5.072	65.750±3.545	27.110	<0.0001*
DIS score at 1wk	21.333±5.125	26.416±8.774	46.250±7.521	29.017	<0.0001*
DIS ≥50% decline	6 (100%)	9 (75%)	1 (20%)	14.000	0.001*
Intellectual disability					
	Moderate (n=5)	sever (n=13)	profound (n=12)	t	p-value
DQ-5 score baseline	34.000±0.707	40.153±4.375	44.166±4.407	11.292	<0.0001*
DQ-5 score at 1wk	12.600±2.073	18.000±6.683	22.083±8.490	3.307	0.052
DQ5≥50% decline	5 (100%)	11 (84.6%)	6 (50%)	6.005	0.050
DIS score baseline	51.400±2.302	57.769±4.985	65.833±3.973	23.068	<0.0001*
DIS score at 1wk	21.600±6.107	29.000±11.965	42.916±10.175	9.137	0.001*
DIS ≥50% decline	3 (60%)	9 (69.2%)	3 (25%)	5.123	0.077

*Significant. CP: cerebral palsy; GMFS: gross motor function system classification; DIS: Drooling impact scale; DQ-5: 5-minute Drooling Quotient.

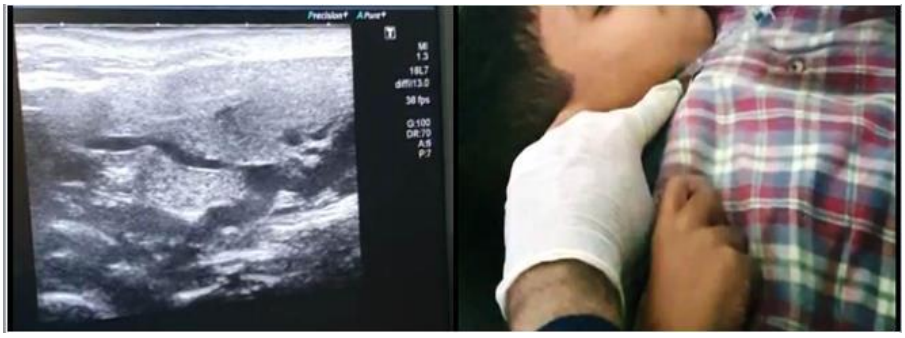


Figure 2. Ultrasound-guided injection into the submandibular salivary gland (case 3)

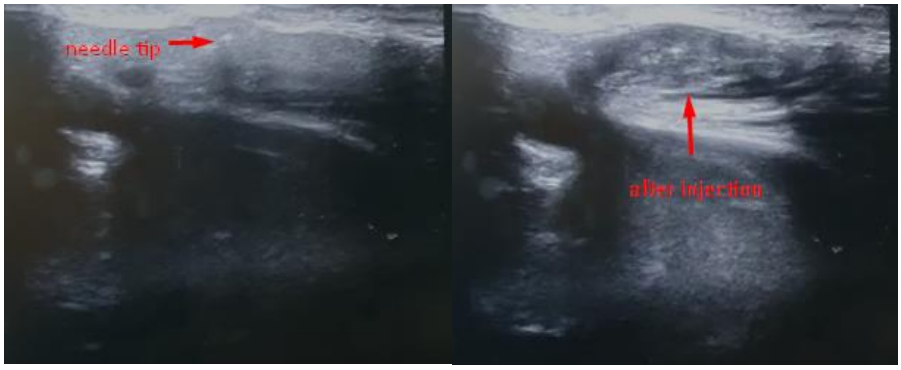


Figure 3. Ultrasound-guided injection before and after injection of botulinum at the parotid gland (case 6)

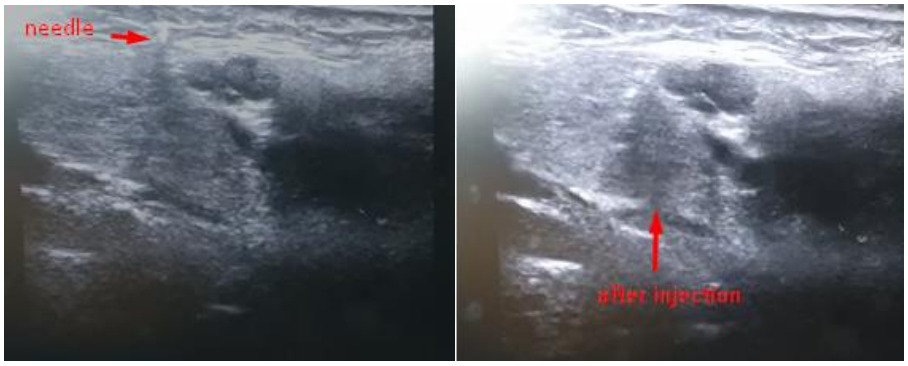


Figure 4. Ultrasound-guided injection before and after injection of botulinum at the parotid gland (case 12)

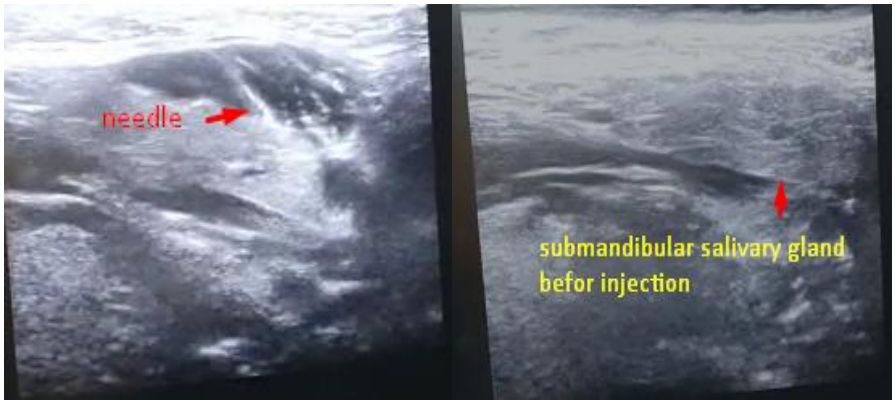


Figure 5. Ultrasound-guided injection into the submandibular salivary gland (case 15)

DISCUSSION

Cerebral palsy children are very heterogeneous regarding their mental and motor capacities. Several factors may influence drooling severity and their response to drooling interventions, including poor seating with the head leaning forward, leading to saliva flow from the mouth by the effect of gravity, nasopharyngeal airway obstruction causing mouth breathing and continuously opened mouth that facilitates the flow of saliva outside the mouth. Dental caries, malocclusions, gum inflammation, and bad oral hygiene also contribute to oral mucosa irritation and increased saliva production [17,18].

Our study demonstrated a significant association between drooling severity and the distribution of spasticity, motor impairment severity, and intellectual disability. Our findings are consistent with Reid, McCutcheon, Reddihough and Johnson [19], who found a significant association between poor gross motor function, intellectual disability, quadriplegic distribution, and drooling in children with cerebral palsy. Poor lip closure and weak control of the face and head muscles are associated with increased drooling in children with neurodevelopmental disabilities. Drooling in children with cerebral palsy is caused by impaired oral motor control but not hypersalivation [20]. Chang, et al. [21] reported that drooling was more severe in children who have the quadriplegic distribution of spasticity than those with diplegic and hemiplegic distribution. Quadriplegic cerebral palsy has more extensive cerebral insult causing greater motor and sensory disabilities, weak motor control, and poor oro-motor and swallowing coordination than those with diplegic cerebral palsy [22].

Our study showed no significant association between the type of cerebral palsy and the severity of drooling. There are controversial reports regarding the association between the types of cerebral palsy and drooling. Hegde and Pani [23] found that children with spastic cerebral palsy have worse drooling than those with athetoid cerebral palsy. In contrast, Erasmus et al. [24] reported that drooling is more severe in children with dyskinetic than those with spastic cerebral palsy. This controversy suggests a complex multifactorial mechanism for drooling in children with cerebral palsy. Adenotonsillar or turbinate hypertrophy, allergic rhinitis, uncoordinated swallowing, and gastroesophageal reflux disease (GERD) may contribute to poor outcomes after salivary control interventions. All those contributors should be assessed and properly managed before intervention. For those with allergic rhinitis, systemic antihistaminic use is associated with decreased salivation [25], so when salivary control intervention, either by botulinum injection or surgery, is recommended close monitoring to evaluate salivary production and response and adjust medical treatment if the patient develops xerostomia. None of our included children had allergic rhinitis. As GERD is a common complication of cerebral palsy, children who have GERD were already on prokinetic medications. However, factors related to the underlying neurological impairment will be difficult to eliminate.

For children treated with botulinum toxin injection, both objective and subjective drooling assessment tests showed significant improvement that extended up to 8 weeks post-injection and remained satisfactory up to 12 weeks either in those who received submandibular glands injection alone or in combination with the parotid glands. This came in accordance with Møller, et al. [26], who found that after follow-up for 20 weeks, the maximum decrease in drooling scores was achieved 8 weeks post-injection into the submandibular salivary gland.

Despite controversy regarding the effective dose, several studies recommend using a dose of 15 units of botulinum toxin to be injected into each gland, the same dose used in our study. Lungren, et al. [27] recommended injection of 15 units per gland for children weighing less than 15 kg, 20 units per gland for weights 15 to 25 kg, and 25 units per gland for weights exceeding 25 kg.

Drooling severity declines significantly in children with cerebral palsy who received botulinum toxin injection either into submandibular glands alone or both submandibular and parotid glands. Therefore, it was not a surprise that improvement was significantly greater in those who received injections into both glands. However, even in those who received injections into submandibular glands bilaterally, the improvement was satisfactory for up to 12 weeks, suggesting that botulinum injection reversibly temporarily affects saliva production. An experimental animal study showed a significant decrease in rats' saliva production that lasted for up to 12 weeks after botulinum injection [28].

Restivo, et al. [29] demonstrated that drooling reduction is strongly correlated to the number of injected glands; injection response was better in those who received when 4 glands than when 3 or 2 glands were injected. Additionally, even after injection of the 4 salivary glands, saliva secretion was sufficient with no impairment of swallowing of food or drinks. This is similar to our findings that swallowing was not impaired; instead, feeding as reported by parents, is less problematic with decreased choking and aspiration. Park, et al. [30] demonstrated that diminished salivary production was achieved 2 weeks after submandibular gland injection and persisted for up to 8 weeks after botulinum toxin injection regardless of the used dose. Çiftçi, et al. [31] reported the effective reduction of drooling in 80% of children with CP after submandibular botulinum toxin injection that continued up to 12 weeks. Suskind and Tilton [32] found that salivary reduction was sufficient in only 30% of children who were injected in the submandibular gland alone, while efficacy increased to 80% when combined injection of both submandibular and parotid glands was done; however, no follow-up was done to demonstrate the maximum duration of improvement.

Van Hulst, et al. [33] reported that drooling severity was decreased in 70% of children with neurodevelopmental disabilities after submandibular glands botulinum injection. This response was maintained up to 32 weeks follow up. The longer duration of improvement in the previous study could be attributed to a larger dose of botulinum injection 25U/gland. Mazlan, Rajasegaran, Engkasan, et al. [34] reported that drooling response was greater in patients who received the high dose of salivary botulinum injection (more than 100 U), with the greatest response maintained up to 24 weeks in those who received a dose of 200 U.

Histological studies demonstrated that salivary gland botulinum toxin injection decreases the size of acinar cells, reducing salivary secretion by these cells. However, this effect is limited to acinar cells at the injection site but does not affect acinar cells away from the site [35]. Furthermore, both parotid and submandibular salivary glands secrete about 95% of daily produced saliva while lingual and minor glands produce about 5% of the daily produced saliva, so decreased salivary production through injection of the 4 glands will never completely abolish salivary secretion [36].

Saliva viscosity may increase due to the anticholinergic effect of botulinum toxin, leading to reflex increased salivary production from other salivary glands, explaining the failure of improvement in some patients after botulinum injection into submandibular glands [37]. This could explain the lower rate of improvement in those who injected into the submandibular glands alone (53%) compared to those who received an injection into both submandibular and parotid glands (93.4%).

Furthermore, botulinum injection induces transient local salivary gland denervation by blocking the synaptic acetylcholine release at the salivary gland [38]. Expression of muscarinic 3 receptor declines at the 1st-week post-injection, then increases gradually 4 weeks later. By the 12th week post-injection, up to 80% of the receptors gained their baseline activity [39-40].

Among our included children, parents were satisfied by the improvement after botulinum injection and preferred to repeat injection rather than doing surgical intervention.

The strengths of this study include the double-blind, randomized design and longitudinal assessment of drooling treatment response over 12 weeks using both objective (5-minute Drooling Quotient) and subjective (Drooling Rating Scale and Drooling impact scale) tools to identify the change in drooling pattern and its impact on the children and their caregivers' daily life. Using ultrasound eliminates failure response due to inadequate injection and allows better evaluation of patient characteristics affecting treatment response. Furthermore, our study demonstrated the efficacy of a low dose of 15 units of botulinum toxin per gland with satisfactory response and no complication for up to 12 weeks, which is well tolerated and financially affordable. However, higher doses may be needed to achieve proper response, so doses should be tailored individually. Alataş, et al. [41] reported that despite decreased drooling in children with CP by 50% after bilateral submandibular salivary gland at a dose 5 units per gland for up to 12 weeks, some patients need higher doses of up to 20 units per gland. Further studies are recommended to evaluate the impact of higher dose versus lower dose regimens on salivary control, dentation, and swallowing and evaluate the impact of different dose regimens on the number of injected salivary glands on short- and long-term outcomes.

Our study has some limitations, including the small number of involved children related to parents' refusal to be involved in this invasive maneuver, which is not widely used in our community. Also, we included children from one center to ensure assessment and intervention by the same physicians to avoid any bias. Another limitation was the missing milder forms of cerebral palsy GMFCS grade 1 and 2, as sialorrhea is less frequent among them. The follow-up duration was too short to evaluate the total improvement period after botulinum injection in cerebral palsy children. Follow-up duration was limited to 12 weeks as most of the previous studies showed temporary improvement for 8-12 weeks post-injection [42].

Furthermore, the pandemic spread of COVID-19 interferes with the expansion of the duration of the study to allow social separation [43-45]. Finally, the evaluation of the viscosity of saliva and the impact of botulinum injection on it was beyond the scope of the current study. Although a reduction in drooling overall may occur, the viscosity of saliva can also change after the injection, which needs further studies to evaluate this point. So, further large-scale longitudinal studies for expanded duration are required to ensure the cause-effect relationship and provide the generality of our findings.

The findings that botulinum toxin injections into all four salivary glands did not impede saliva secretion or swallowing highlight a critical aspect of treatment safety and efficacy. Parents reported a reduction in feeding difficulties, with fewer instances of choking and aspiration, suggesting that the treatment not only mitigates the symptoms of sialorrhea but also preserves essential functions necessary for safe swallowing of food and drinks. This balance between reducing excessive saliva and maintaining sufficient saliva production is vital for ensuring that children with cerebral palsy can safely consume a variety of foods, including those functional foods rich in bioactive compounds, without the risk of swallowing difficulties. In the evolving landscape of nutritional science, the Functional Food Center (FFC) has refined its definition of functional foods to better capture their impact on health. The updated definition, which emphasizes the presence of biologically-active compounds in natural or processed foods, underscores the clinically proven health benefits they provide [46]. Such foods, defined by specific, effective, and non-toxic amounts of these compounds, are recognized for their role in promoting optimal health and managing the symptoms of chronic and viral diseases [46]. FFC sets the

stage for discussing the significance of functional foods in relation to managing conditions like cerebral palsy, where the modulation of diet can have profound implications for health and quality of life. For instance, within the context of cerebral palsy management, the role of bioactive compounds extends beyond nutrition to include antimicrobial activity that can safeguard against the heightened risk of oral infections such as Candida infection [47]. This is particularly relevant for children with sialorrhea, who may face challenges with oral hygiene due to excessive salivation [47]. Incorporating propolis, a substance rich in bioactive compounds, could potentially offer antimicrobial benefits, thereby reducing this risk and contributing to the overall health regimen for managing cerebral palsy [48].

This study suggests a novel, synergistic approach where botulinum toxin treatment for sialorrhea is complemented with a tailored dietary plan that emphasizes functional foods. This integrated strategy could lead to a dual benefit: improved management of sialorrhea and optimized intake of nutrients critical for this demographic. The bioactive compounds in these foods have the potential to not only improve general health but also to address specific symptoms and complications associated with cerebral palsy. Furthermore, this approach aligns with the goal of leveraging specific biomarkers for promoting optimal health, offering a holistic strategy that goes beyond symptom management to enhancing overall wellbeing. Implementing such an approach requires a multidisciplinary effort, involving neurologists, dietitians, and caregivers, to ensure a diet that is not only high in specific bioactive compounds but also palatable and acceptable for children with cerebral palsy, thus encouraging regular consumption and maximizing health benefits.

CONCLUSION

Injecting botulinum toxin into the submandibular salivary glands alone can effectively reduce drooling in children with cerebral palsy. However, when combined with injections into the parotid glands, the response is even better and lasts for at least 8 weeks without any complications. It's important to note that children with grade 5 GMFS, intellectual disability, and quadriplegic distribution may not respond as well to botulinum toxin injections, indicating the need for alternative treatment strategies for their drooling.

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Abbreviations: ENT. ear, nose and throat, DIS. Drooling impact scale, DQ-5. Drooling Quotient, GERD. gastroesophageal reflux disease, GMFCS. Gross Motor Function Classification System, SPSS. statistical package for social sciences

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