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Use of botulinum neurotoxin A in uncontrolled salivation in children with cerebral palsy: a pilot study

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Abstract. This study investigated the safety and efficacy of botulinum neurotoxin type-A (BNT-A) injections into the salivary glands for treatment of sialorrhea in children with cerebral palsy (CP) and assessed the clinical factors that affect treatment outcome. The parotid and submandibular glands of nine CP patients were injected with BNT-A 1.4 U/kg in each parotid gland, and 0.6 U/kg in each submandibular gland. All children had neurological disorders. Gross motor function classification system levels ranged from I to V. All children had moderate to severe intellectual disability. A telephone interview with one parent determined response to treatment. Drooling intensity and frequency were measured with the drooling severity and frequency scale. After BNT-A treatment, the patients were followed up for 6 months using self-assessed rating scales for drooling intensity, discomfort and treatment effect (drooling impact scale). All parents reported an improvement in sialorrhea in the first week. Drooling was very intensive at baseline, and moderate 2 weeks after treatment. Maximum response occurred at 2–8 weeks. The use of BNT-A in uncontrolled salivation in children with CP can be considered acceptable and effective. Malocclusion and anterior salivation are closely related clinical characteristics and should be taken into account when planning treatment.

Key words: botulinum neurotoxin type-A; BNT-A; sialorrhea.

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Xerostomia is one of the first manifestations of botulism, which prompted investigations of its application for treating drooling. Botulinum neurotoxin (BNT) was the first bacterial toxin used as a medicine. Its clinical applications have been expanding over the last 30 years and novel possibilities are reported.[1–3] Acetylcholine acts as a neurotransmitter for innervation of muscles and gland tissues. Blocking the release of leads to a reduction in pathological movements of muscles and secretion of glands.[3,4] Intraglandular delivery of botulinum neurotoxin type-A (BNT-A) inhibits the release of acetylcholine from cholinergic nerve endings and consequently reduces the secretion of saliva and diminishes drooling in the majority of patients.[1,4,5] It has a temporary paralytic effect.

Insufficient control of the coordinate mechanism of the orofacial, palatolingual, and head and neck musculature results in excessive pooling of saliva in the anterior part of the oral cavity and unintentional saliva loss.[6,7] The problem is mostly related to

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disturbed glutition rather than hypersalivation in children with cerebral palsy (CP).

BNT-A is used in uncontrolled salivation in neurologically impaired children.[8–11] Drooling is a significant disability for a large number of paediatric patients with CP and other types of neurological and cognitive impairment.[12–15]

A number of treatments have been developed to reduce it. Oral-motor programmes to improve oral-motor function are essential initially if there is patient compliance. The possible pharmacological approaches include anticholinergic drugs.[16–18] Surgical treatment remains the last resort for patients with profound sialorrhea who have failed conservative management. Submandibular duct relocation with simultaneous sublingual gland excision remains the procedure of first choice for persistent significant drooling.

Simultaneous ligation of the submandibular and parotid ducts is promising. A recent initiative to inject the major salivary glands with BNT is being evaluated.[19–23] Many factors contribute to the passage of saliva from the oral cavity to the oesophagus, such as the child's mental abilities, the cognitive awareness of social norms, an intact swallowing mechanism, oral sensibility, lip closure, and the ability to hold the head in an upright position. Sialorrhea is a problem which can lead to many complications, such as aspiration pneumonia, skin maceration, and dental caries.[6,7,10,23] The constant presence of saliva may impair articulation and effective communication. All of these complications negatively affect the quality of life of patients and their families. Uncontrolled salivation affects the child and the family and caretakers, decreasing their quality of life.

With respect to aetiology and clinical impact, it is advisable to distinguish anterior drooling from posterior drooling.[7,10] Saliva spilled from the mouth is referred to as anterior drooling, which is clearly visible. In the case of posterior drooling, saliva is spilled through the faucial isthmus creating a risk of aspiration. Inadequate lip closure, habitual open-mouth posture, ineffective or limited tongue movements, poor coordination between the oral and pharyngeal stages of swallowing, malocclusion, flexed posture, gingivitis and dental caries may contribute to the origin of drooling.

The aim of the present study was to investigate the safety and efficacy of BNT-A injections into the salivary glands for treatment of sialorrhea in children with CP and to elucidate the clinical factors that play a role in the outcome of the treatment.

Table 1. Drooling severity and frequency scale (DSFS).[20]

Drooling severity scale
1 = Never drools, dry
2 = Mild – drooling, only lips wet
3 = Moderate – drool reaches the lips and chin
4 = Severe – drool drips off chin and onto clothing
5 = Profuse – drooling off the body and onto objects (furniture, books)
Drooling frequency scale
1 = No drooling
2 = Occasionally drools
3 = Frequently drools
4 = Constant drooling

Table 2. Questionnaire-based scoring system for drooling severity and frequency according to DSFS.[20]

	Drooling severity (Average)	Drooling frequency (Average)	DSFS (Average)
Baseline	4.3	3.3	7.6
Week 2	2.3	1.8	4.1
Week 4	2.3	2	4.3
Week 6	2.4	2	4.4
Week 8	2.7	2.2	4.9
Week 10	3.2	2.8	6
Week 12	3.8	3.3	7.1

Patients and methods

12 children were identified with CP, three of them were excluded because their parents declined to participate in the study. Nine paediatric patients with CP (four male and five female, aged 1.6–11 years, weight 10–30 kg), admitted to the Department of Neurology and Neurorehabilitation of the Children's Clinic of Tartu University Hospital, were screened from January 2011 to August 2011. All children had moderate to severe intellectual disability and three of them had epilepsy. Four children had spastic and five had dyskinetic movement disorder: four of them were wheelchair dependent. In four cases the aetiology of CP was birth hypoxia. The study was approved by the Ethics Committee on Human Research of the University of Tartu (protocol No. 192/T-3; 26.04.2010). The parents' written informed consent was obtained. Children with moderate and severe sialorrhea were enrolled in a descriptive, non-blinded prospective study. The present study evaluates several clinical factors that play a role in the outcome of drooling treatment. These clinical parameters are dental status, malocclusion, oral motor performance, mouth closure, lip seal, anterior or posterior drooling, speech, and swallowing.

All patients had oral motor hyper-tonicity and eight of them had slow uncoordinated tongue movements, insufficient lip closure and malocclusion (mostly open bite). Four children had breathing problems because of saliva aspiration and two of them needed a tracheostomy. A gastrostoma was used due to feeding and swallowing difficulties in four cases. Anterior drooling occurred in five cases, posterior drooling in three cases, and one patient had both.

Evaluation of drooling

In all enrolled children, drooling was evaluated subjectively and objectively using standardized parameters. Subjective evaluation was rated by the parent or caregiver using the drooling severity and frequency scale (DSFS[20]) which summarizes severity and frequency subscores (Tables 1 and 2). This scale quantifies the severity and frequency of sialorrhoea on a scale of 2–9. The domain specifically focusing on the severity of drooling ranges from one (no drooling) to five (profuse drooling). The domain for frequency ranges from one (no drooling) to four (constant drooling).

Visual analogue scales (VAS[11]) rating the parents' opinion were applied. Evaluation of drooling frequency by VAS was measured according to the number of bib changes per day (Table 3) and the number of cases needing aspiration per day (Table 4). A detailed questionnaire was developed to evaluate the impact of drooling on the items of daily life.[24] Table 5 shows the sensitivity of the drooling

Table 3. Data for the subjective evaluation of drooling by the number of bib changes per 24 h.

Patient	Evaluation (bibs/24 h)	Baseline	Weeks								
			2	4	6	8	10	12	14	16	18
1	Bib change	6 or 7	5 or 6	5 or 6	5 or 6	5 or 6	6	No effect			
2	Bib change	2	1	1	1	1 or 2	1 or 2	No effect			
4	Bib change	10	3	3	2	2	2	4 or 5	No effect		
5	Bib change and aspiration	4 or 5	1	1	1	3 or 4	No effect				
6	Bib change and aspiration	10	4 or 5	4 or 5	4 or 5	4 or 5	5 or 6	6 or 7	7 or 8	No effect	
7	Bib change	4 or 5	1	0 or 1	0 or 1	0 or 1	0 or 1	0 or 1	1 or 2	3 or 4	3 or 4
8	Bib change	8	8	No effect							
9	Bib change and aspiration	1 or 2	0	0	0 or 1	0 or 1	0 or 1	0 or 1	1 or 2	3 or 4	3 or 4
Average		5.875	3	2.937	2.875	3.313	3.625	4.25	5.188	5.75	

impact scale. To assist evaluation of the clinimetric properties of the scale, the parents or caregivers were also asked to rate, on a four-point scale, the degree to which drooling had increased or decreased after treatment, as well as the accompanying quality of life. A score of four was categorized as significant reduction in drooling, three as marked reduction, two as moderate reduction, one as mild reduction and zero as no reduction.

The inclusion criteria were: children of pre-school and school age; confirmed neurological diagnosis (clinically, computed tomography, magnetic resonance imaging, and EEG); a score of three or higher on the DSFS indicating moderate and severe drooling; all medications taken for drooling were stopped at least 3 months before the beginning of the study; minimal body weight 10 kg; informed consent; caretakers with sufficient cognitive ability to participate in the study; readiness to participate for at least 12 months. The exclusion criteria were: enrolment of the child in another medical study; previous surgical procedures in the oral or nasal cavity interfering with saliva production; treatment with BNT-A for another indication during the previous 6 months; neuromuscular disorders; use of drugs interfering with saliva secretion; known systemic diseases (bronchial asthma, congenital heart failure and myasthenia gravis). To determine the children's responses to this therapy, a structured telephone interview with one parent or legal guardian (drooling impact scale) was conducted every second week after the injection.

BNT-A injection into the salivary glands

All BNT-A injections into the submandibular and parotid glands were performed by one team (a radiologist and a maxillofacial surgeon) over a 1-year period from 2010 to 2011. For the procedure, general anaesthesia was used in seven children. In two children the injections of BNT-A were made with the application of anaesthesia with Ung lidocaine hydrochloride 5% (Ung. Emla®). Ultrasound guidance was used to place 27-gauge needles in the anteroposterior direction into each submandibular and parotid gland. The 7.5 mHz linear transducer was positioned in such a way that it was possible to perform an injection with the needle directed along the longitudinal axis of the transducer, providing a quick and easy to perform visualization of the needle in the gland. A solution of 100 units of BNT-A (Botox®, Allergan) was prepared in a 2.5 ml volume of normal saline. The recommended dose for Botox® (Allergan) was weight-dependent: 1.4 U/kg in each parotid gland, and 0.6 U/kg in each submandibular gland was inserted under ultrasound control. The patients were followed up every second week up to week 16.

During the study, no medication that could influence the severity of drooling was allowed. Possible adverse effects and risks related to the interventions during the study were explained to the parents. To determine the children's responses to this treatment, a study was designed using a structured telephone interview with one parent or guardian for each child. The schedule of the interview was developed on the basis of a literature review and experience.[25]

The initial patient interview included a thorough evaluation of the medical and social-emotional history of the patient and consideration of aetiology. Drool reduction, need for suctioning and bib changes, respiratory distress, quality of life, and complications such as facial swelling and swallowing dysfunction were included in the final schedule of the interview. Drooling severity at baseline and reduction in sialorrhea during treatment were measured using a parent questionnaire. After the BNT-A treatment, the patients were followed up for 6 months with evaluation every second week by means of self-assessed rating scales[20] for drooling intensity, discomfort and treatment effect. The parents were also asked to record the adverse effects of the BNT injections in a diary.

Results

Sialorrhea was closely related to the clinical factors. Eight of nine patients had anterior open-bite and open mouth and only one patient had sealed lips. Three of nine patients could hold their head, none of the patients could control their voluntary tongue movements, and all patients had mental age recession. Eight of the nine were not able to speak, and one child had speech disturbance.

All patients reported a direct decrease in drooling after the injection. Almost all patients reported a subjective improvement in sialorrhea in the first week, and objective improvement according to the DSFS and the number of bibs used per day. All patients had thickening of saliva about 2 weeks after the BNT-A injection. Drooling was very intensive at baseline; 2 weeks after treatment the parents reported moderate drooling. The data of the subjective evaluation of the patients' average

Table 4. Data for the subjective evaluation of drooling by the number of aspiration per 24 h.

Patient	Evaluation (aspiration/24 h)	Baseline	Weeks								
			2	4	6	8	10	12	14	16	18
3	Aspiration	7	3	3 or 4	3 or 4	3 or 4	3 or 4	4	4	4	4
5	Bib change and aspiration	5 or 6	3	2	2 or 3	3 or 4	4	No effect			
6	Bib change and aspiration	1 or 2	0	0	0 or 1	0 or 1	0 or 1	No effect			
9	Bib change and aspiration	1 or 2	0	0	0 or 1	0 or 1	1	No effect			
Average		3.875	1.5	1.375	1.750	2	2.250	3.125			

drooling, using the DSFS, is presented in Table 2.

Five of the nine patients needed only bib change, one patient needed only aspiration and three patients needed both bib change and aspiration in their daily life (Tables 3 and 4).

Maximum response to the BNT-A injection was noted at 2–8 weeks. The average need for bib change decreased from 5.875 times at baseline to three times at 2 weeks after the injection, to 2.937 times at 4 weeks after the injection, to 2.875 times at 6 weeks and to 3.313 times at 8 weeks after the injection. The average need for suctioning decreased from 3.875 times at baseline to 1.5 times at 2 weeks, to 1.375 times at 4 weeks, to 1.75 times at 6 weeks and to 2 times at 8 weeks. One child showed no response to the BNT-A injection. In two children the positive effect was observed also at 18 weeks. One child had difficulties with swallowing for 3 weeks. There were no complaints of pain or swelling in the study group.

The drooling impact scale assessed the change in the caregiver's quality of life. Three caregivers reported a significant increase in their quality of life (four points), three caregivers reported a marked increase (three points), two reported a moderate increase (two points) and one did not see a change in her quality of life (zero points); no caregiver reported a minor increase (one point). The average increase in quality of life was 2.778 points (Table 5). The effect reached a maximum in the first 2 months and decreased thereafter.

Table 5. Results of the evaluation of the patients' quality of life.

Patient	Quality of life	Points (0–4)
1	Marked increase	3
2	Marked increase	3
3	Marked increase	3
4	Moderate increase	2
5	Moderate increase	2
6	Significant increase	4
7	Significant increase	4
8	No increase	0
9	Significant increase	4
Average		2.778

As the procedure is invasive and the positive effect only lasts for the first 2 months, the parents preferred this treatment option in the winter period when there are more respiratory infections associated with saliva-soaked clothes.

Discussion

Excessive drooling is common in children with chronic neurological disorders. It can be a serious social disability impeding social interaction and greatly reducing the quality of family life. Preliminary observations suggest that injections of BNT-A into the salivary glands can decrease drooling, but the optimal dose,[7,13,18] sites of injection,[6,8,11,21] and definition of clinical factors that influence the therapy outcome of BNT-A injections for drooling[26] have not been established. It appears that the widely ranging dosages of BNT may be influenced by type of the patient, severity of sialorrhea, injection technique, personal preference and experience of the physician.[5,27] Data about the optimal doses of BNT are discordant. Several studies have shown that the effect is dosage related and it has been concluded that insertion of higher doses of botulinum neurotoxin into the parotid glands or concomitant injections into the submandibular glands can increase the efficacy of these injections.[8,18] An increase of side effects has been reported as well.[18,28]

The present findings indicated that the weight dependent dose of BNT-A under ultrasound guidance into both submandibular and both parotid glands was effective in 89% of cases. Earlier results of the Jongerius research group showed that up to 30–50% of patients did not respond to submandibular injection of BNT-A[9,10,18] and Hassin-Baer et al. reported poor results after injecting 5–10 U into each parotid gland.[8]

The present result is in concordance with previous studies by Suskind and Tilton[29] and Banerjee et al.,[25] who suggested that the response rate can increase up to 90% when injecting the submandibular and parotid glands bilaterally.

Ultrasound guidance during the injection procedure is a simple method for targeting the gland. It also provides correct positioning of the needle in the gland and reduces side effects related to injections into the adjacent muscles, vessels or nerves. Generally, the effect of injecting BNT-A into both submandibular and both parotid glands under ultrasound guidance lasted for about 3 months.[13,14,29] Salivary flow rates usually dropped sharply within 1 week after the injection but rose again after 12 weeks. In this study, high salivation rates returned after 3–4 months.

Available information for providing recommendations about the timing of intervention of BNT-A injection to maintain the therapeutic effect is too scanty, but there should probably be a 4- to 6-month interval between each treatment. Repeated injections with an interval of less than 3 months enhance the risk of antibody formation.[7,19]

Some of the earliest articles describe the presence of adverse effects such as dysphagia, sialoadenitis, xerostomia and chewing difficulties.[3,14,30]

Several studies have reported no side effects,[19,29,31,25] but one patient in the present study had swallowing problems for 3 weeks and in six patients thickening of saliva lasted for 8 weeks.

All patients in the present study experienced a marked improvement in their quality of life. The results of this study would help improve the quality of care of children with sialorrhea. Injecting BNT-A into the salivary glands for drooling might have a therapeutic benefit for paediatric CP patients with limited adverse reaction.

To the best of the authors' knowledge, few studies have analyzed clinical factors (head position, lip seal, voluntary control of tongue movements, control of voluntary movement functions, and mental age) influencing the treatment outcome. For example, head position and lip seal are influenced by gravity. The same also applies to movement function which is clearly related to the head position. Previous studies have demonstrated that tongue mobility is strongly correlated with drooling and drooling control. There is evidence that the activity of the hypothalamic–pituitary axis is altered in children with neurological disabilities. The therapy outcome of submandibular BNT-A could also be influenced by compensatory strategies of the central circuitries responsible for saliva production.[26,32]

The results showed an increased prevalence of malocclusion in children with CP. Children with CP are likely to have a significantly increased anterior open bite. Thus occlusion and anterior salivation are closely related. Patients with occlusion abnormality frequently have anterior drooling. Biting problems are largely caused by habits. Impaired children have weak head and neck musculature and glutition is disturbed. Usually, breathing through the nasal cavity is changed to mouth breathing at rest. This is why these children hold their mouth open at rest, and saliva spills out. They often have respiratory tract infections because of hypersalivation into the oral cavity; the mucosa swells and nasal breathing is disturbed. Oral hygiene is not good because of motor dysfunction, which causes deposition of dental calculus, caries problems and earlier teeth loss, which results in biting problems.

All patients in the study group were predisposed to diseases and had frequent respiratory tract infections. As BNT-A injection is expensive and is carried out under general anaesthesia in most cases, which makes the procedure more invasive, calculation of its cost effectiveness is necessary.

There is a great need for further research to evaluate the relationship between occlusion and posterior drooling. This study group was too small to draw relevant conclusions. In most cases anterior and posterior drooling were combined. There was one patient with posterior drooling alone. She was the only patient who had normal occlusion without caries and calculus. Although she was able to hold her lips sealed at rest, she had severe breathing problems and infections related to saliva aspiration.

As the studied set of clinical variables did not allow the prediction of which children would be responders, the opposite can also be true. Children with one or more clinical factors (head position, lip seal, voluntary control of tongue movements, control of voluntary movement functions, and mental age) can still have a positive clinical outcome. Therefore, randomized controlled trials are required to address specific questions related to the clinical factors of patient selection such as: occlusion and posterior drooling, repeated injections and treatment response.

It should be noted that the findings of this short term study are preliminary, long-term investigation and a larger number of paediatric patients with CP are required to improve their validation. Ongoing and future research will help to define standardized treatment protocols to further improve the quality of life in children with CP.

In conclusion, the use of BNT-A in uncontrolled salivation in children with CP can be considered acceptable and effective. Malocclusion and anterior salivation are closely related clinical characteristics and should be taken into account when planning treatment.

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None declared.

Competing interests

None.

Ethical approval

This study was approved by Ethic Committee of Human Research of University of Tartu (protocol No. 192/T-3).

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