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Treatment of sialorrhoea with repeated ultrasound-guided injections of botulinum toxin A into the parotid and submandibular glands

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Abstract

Botulinum toxin injections are useful in patients with refractory sialorrhoea although the optimum treatment protocol and its efficacy over a long period of follow up are controversial. The aim of our prospective study was to examine the efficacy and complications of a protocol of repeated ultrasound-guided botulinum toxin injections of fixed doses at a tertiary children's hospital. A total of 79 procedures were done in 34 patients who were followed up for two years. The overall complication rate was 3%. The outcome measures considered included the Drooling Frequency Severity Scale (DFSS), visual analogue scale (VAS), and carers' assessments of the reduction in drooling. Our study highlighted two types on non-responders (primary and secondary) of which 3/34 required definitive surgical management. In summary, this study shows that a protocol of repeated injections of fixed doses of botulinum toxin A, while not beneficial in all cases, is a potentially valuable option for the safe and effective treatment of sialorrhoea in children.

Keywords: Sialorrhoea; Botulinum Toxin; Drooling; Paediatric

Introduction

Pathological drooling beyond the age of 4 years is a serious clinical, social, and emotional issue for children and their carers. Chronic sialorrhoea can lead to local irritation of skin and recurrent aspiration pneumonia, and can interfere with the development of speech.[1] It is the consequence of an uncoordinated swallowing mechanism in the oral phase,[2] and affects 10% of patients with an underlying neurological disorder such as Parkinson's disease or cerebral palsy.[3] In special needs schools, 33% of pupils suffer from severe drooling.[4] Treatments were initially limited to surgical options in refractory cases, or anticholinergic medications that can have systemic side effects and behavioural modifications, which limit their value in children with severe learning difficulties.[5]

The use of botulinum toxin for the management of sialorrhoea was first proposed in 1997,[6] and botulinum toxin A (BTX-A), one of the seven proteases (A-G), is now commonly injected into the salivary glands for treatment. It binds to SNAP-25 (25kDA synaptosome-associated protein) and disrupts the fusion of vesicles in the presynaptic membrane, and the secretory pathway for acetylcholine. This chemodenervation is reversed only when the nerve ending regenerates

Abbreviations: BTX, Botulinum; DFSS, Drooling Frequency Severity Scale; VAS, Visual Analogue Scale; WRST, Wilcoxon Signed Rank Test.

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with the target organ again,[7] although a temporary reduction in drooling can be found up to 24 weeks after the intervention, with initial response rates of up to 80%.[8,9] Ultrasound-guided injections, which are more accurate than blind injections, have improved the efficacy, with a considerably greater reduction in saliva in the first week.[10,11]

This prospective study examines the effects of repeated ultrasound-guided BTX-A injections into the parotid and submandibular glands at a tertiary children's hospital.

Method

This prospective study was conducted at Alder Hey Children's Hospital between February 2012 and April 2014. All patients had previously had conservative treatment with no satisfactory reduction in drooling. Those who had a history of allergy to botulinum toxins, or profound atrophy or weakness of the facial muscles, were excluded, as were those whose carers did not consent.

All procedures were done under general anaesthetic by an ear, nose, and throat (ENT) surgeon, with ultrasound imaging by a head and neck radiologist. Fifteen units of BTX-A allergen were divided between two sites in both the parotid and submandibular glands using a 21-gauge needle under ultrasound-guidance (linear high frequency transducer 12-15 MHz). Each patient had a total dose of 60 units. Patients were observed postoperatively for at least two hours before being discharged, and were typically followed up one month and six to eight months after each procedure.

Wilcoxon signed rank tests were used to compare the baseline drooling frequency and severity scores (DFSS) and visual analogue scale (VAS) drooling scores with their mean counterparts at one month and at subsequent follow ups. Probabilities of less than 0.05 were considered significant. All statistics were analysed with the help of IBM SPSS Statistics for Windows version 22 (IBM Corp).

Questionnaire

To gather evidence of the efficacy of the injections, we used an online survey questionnaire before, and at one month after, the intervention, and a repeat questionnaire before the next injection. All of them were filled out by carers or guardians. Methods that have been used to measure salivary outflow objectively have shown poor reproducibility and have failed to acknowledge variations in salivary flow throughout the day.[12] We therefore did a descriptive systematic review of key studies in the field before developing our questionnaire. From this we derived five main outcome measures/intervention (Table 1).

This was similar to several studies in the field and aided comparison of regimens.[13] The DFSS is the outcome measure used most commonly and is sensitive enough to detect observed changes in drooling (Table 2).[14] We also recorded baseline details such as age, sex, and coexisting conditions, together with the carers' satisfaction with the service.

This service evaluation was formally registered within the trust in line with local governance protocols. All data were anonymised and stored on a secure Microsoft Access Database on the hospital server.

Table 1
Five main outcome measures/intervention.

- Severity of drooling (1 = low to 5 = high)
- Frequency of drooling (1 = low to 4 = high)
- Visual analogue drooling scale (1 = no drooling to 10 = worst drooling)
- Carer-assessed reduction in drooling (0 = no reduction to 10 = no drooling)
- Therapeutic window for each intervention

Table 2
The drooling frequency and severity score (DFSS).

Frequency	
1	Never
2	Occasionally (not every day)
3	Frequently (part of every day)
4	Constantly
Severity	
1	Dry (never drools)
2	Mild (only lips wet)
3	Moderate (wet on lips and chin)
4	Severe (drool extends to wet clothes)
5	Profuse (hands, tray and objects wet)

Results

Thirty-four patients were enrolled during the observed period (Table 3). One had to be excluded as the questionnaire was incomplete. Of these, fourteen patients completed the online questionnaire at one month. A total of 79 procedures were done during the observed period, and 21 patients had more than one intervention (Fig. 1). The mean (range) age of the group was 11 (1–23) years, with a mean (range) weight of 28.3 (8.6–74.3) kg. Seventeen patients were female and 16 male. The most common coexisting conditions were syndromic or general developmental abnormalities (n = 19), followed by cerebral palsy (n = 13) and epilepsy (n = 11).

The technique was successful and there was only one temporary complication of dysphagia. The child had been fed through a percutaneous endoscopic gastrostomy (PEG) tube before treatment and was allowed to have solid food in limited quantities, but this deteriorated for six weeks and then promptly recovered.

The intervention was at least partly effective in 30 patients. The three patients who reported no reduction in drooling after only one treatment went on to have definitive operations (relocation of a submandibular duct or excision of the submandibular gland). It is worth noting that in a small number of patients (n = 3), the first intervention reduced drooling

Table 3
Age, sex, coexisting conditions, and results of botox intervention.

Age (years)	Sex	Coexisting conditions	No. of interventions	Baseline drooling severity (5)	Baseline drooling frequency (4)	Mean drooling severity after intervention	Mean drooling frequency after intervention	Mean reduction after intervention
9	F	Beckwith-Wiedemann syndrome, gross developmental delay, and scoliosis	3	5	4	4	3	9.3
14	F	None relevant	1 (relocation of SM ducts)	3	3	3	3	0
22	F	Cerebral palsy and global developmental delay	3	5	4	2.3	2	8.7
12	F	Oral-facial digital syndrome type 1, epilepsy, global developmental delay, and recurrent chest infections	2	3	3	4	3	6.5
5	F	Chronic lung disease, tracheobronchomalacia (tracheostomy in situ), severe gastro-oesophageal reflux (fundoplication and PEG fed), and epilepsy	2	3	3	4.5	3.5	1
10	M	Subaortic fibromuscular obstruction, aortic regurgitation, chromosomal translocation (15/22), and gastro-oesophageal reflux	10	5	4	3	2.5	7.3
18	F	Severe learning difficulties, cerebral palsy, dystonia, perinatal intracranial haemorrhages, epilepsy, fundoplication and gastrostomy, cortical visual impairment, VP shunt and precocious puberty	2	4	3	2.5	2.5	9
10	F	Global developmental delay and learning difficulties	5	4	4	3	3.6	6.4
9	M	Cerebral palsy	1	5	4	3	3	8.0
12	F	Cerebral palsy, epilepsy, PEG fed, tracheostomy, recurrent chest infections, and severe scoliosis	2	5	4	4	4	5.0
18	F	Epilepsy, developmental delay, and learning difficulties	4	5	4	4.8	4	7.5
8	F	Lissencephaly and schizencephaly, Lennox-Gastaut phenotype, global developmental delay, and gastro-oesophageal reflux (fundoplication)	3	5	4	4	3.3	10.0
11	M	Cerebral palsy and epilepsy	3	5	4	3.3	4	2.3
19	M	Cerebral palsy and scoliosis	3	4	4	1.7	3.3	9.3
23	M	Cerebral palsy and epilepsy	2	4	4	4	3.5	3.5

10	F	Aicardi syndrome, severe developmental delay and recurrent chest infections	1	5	4	5	4	10.0
7	M	Ex-prematurity, cerebral palsy, on non-invasive ventilation, and severe gastrointestinal dysmotility	2	4	3	2	1	10.0
10	M	Cerebral palsy and epilepsy	2	5	4	4.5	3	9.0
7	F	Epilepsy, developmental delay, and chromosomal anomalies	1	5	4	5	3	1.0
10	M	ALL (remission), learning difficulties, and epilepsy	5	4	3	4.3	3	5.8
10	M	Cerebral palsy, developmental delay, partial visual impairment, and scoliosis	3	5	4	4.7	4	5.0
8	M	17q deletion syndrome and recurrent croup	2	5	4	1.5	1.5	6.0
5	M	Right total retinal detachment, congenital sensorineural deafness, cerebral hypoplasia, microcephaly, developmental delay, and epilepsy	1	4	4	3	2	4.0
10	M	Cerebral palsy, agenesis of the corpus callosum, right-sided lissencephaly, tracheal stenosis (tracheostomy), and small bowel dysmotility	2	4	4	3	3	8.5
18	M	Lennox-Gastaut syndrome and severe learning difficulties	1- SM gland excision	5	4	4	4	0
14	M	Cerebral palsy, epilepsy, constipation and PEG fed	4	5	4	3.5	3.25	7.0
10	M	None relevant	1	4	3	4	3	9.0
8	F	Pfeiffer syndrome, choanal atresia, tracheostomy, Chiari malformation, VP shunt, developmental delay and gastro-oesophageal reflux (fundoplication and PEG)	1	5	4	4	4	5.0
7	F	Worster-Drought syndrome and global developmental delay	3	4	4	3.7	3.7	7.7
7	F	Cerebral palsy, and gastrostomy fed	1	4	4	3	3	10
7	F	Worster-Drought syndrome and learning difficulties	1-relocation SM ducts	5	4	4	4	0
17	F	Down syndrome, scoliosis and hypothyroidism	1	5	4	3	3	4
1	M	Developmental delay, tracheostomy and long-term ventilation	1	4	4	5	4	5

SM = submandibular gland; ALL = acute lymphoblastic leukaemia; PEG = percutaneous endoscopic gastrostomy; VP = ventriculoperitoneal shunt.

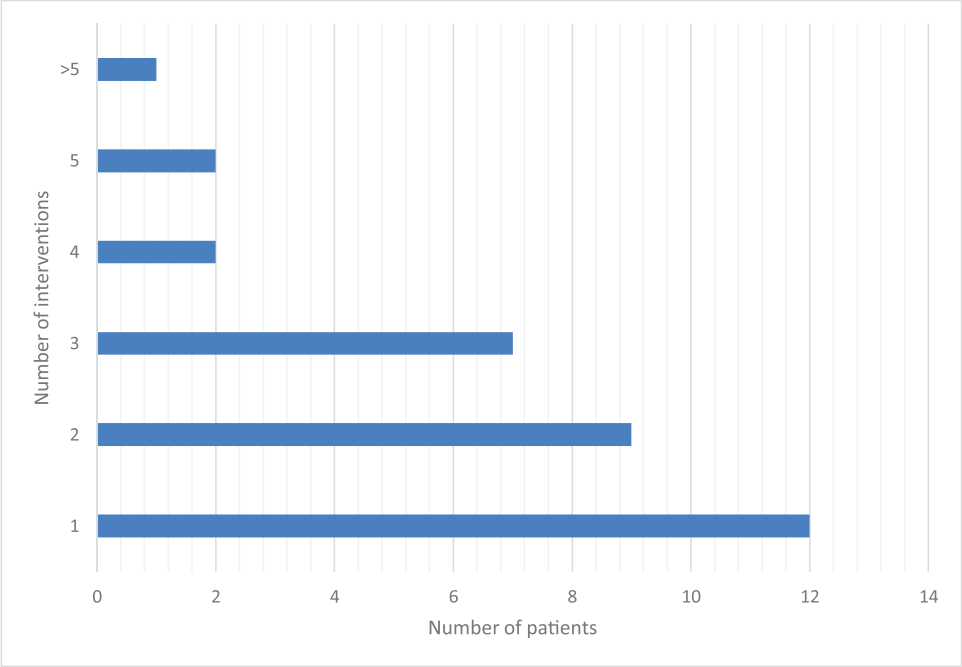

Fig. 1. Number of patients in each intervention group. The patient who had more than 5 interventions actually had 10 BTX-A treatments in total.

Table 4
Mean scores for severity and frequency of drooling, and visual analogue scores (VAS) of 33 patients.

	Baseline	1-month follow up	Reduction from baseline (%)	p value	Total mean follow up scores	Reduction from baseline (%)	p value
Severity of drooling	4.45	3.02	32.1	0.00	3.60	19.1	0.00
Frequency of drooling	3.76	2.86	23.9	0.02	3.11	17.3	0.00
VAS (1 = no drooling and 10 = worst drooling)	7.84	4.47	43.0	0.12	6.26	20.2	0.11

but the second did not. Spearman's rank correlation coefficient of 0.11 between weight and reduction in drooling at the first intervention did not show any significant association.

The mean interval between injections was 7.3 months. Carers noticed a reduction in drooling in a mean (range) of 1.5 (0–5) weeks after the intervention, and its effect lasted for a mean (range) of 3.5 (0–12) months (Fig. 2). The greatest duration of therapeutic effect was noted after three interventions (20 weeks).

The Wilcoxon signed rank test was used to compare the baseline scores for frequency and severity of drooling, and VAS for drooling, with the corresponding one-month follow up and subsequent mean follow-up scores. All three measures showed that injection of BTX-A significantly ($p < 0.05$) reduced drooling both at one month and at subsequent follow ups (Table 4).

The carer-assessed drooling score showed a reduction after both single and multiple interventions (Table 5). As part of our questionnaire we asked carers whether sialorrhoea influenced their decisions to take their child outside. Initially, 26/33 carers answered "No", but after the intervention this increased to 24/28. Overall, 33/34 carers were satisfied with the service.

Table 5
Mean reduction in drooling scores for each BTX-A intervention.

No. of interventions	No. of patients	Mean (range) reduction in drooling score (0 = no reduction, 10 = no drooling)
1	33	6.27 (0–10)
2	21	6.10 (0–10)
3	12	7.67 (2–10)
4	5	6.20 (2–8)
5	3	6.67 (4–9)
>5	1	8.80 (8–9)

Discussion

Many authors have acknowledged a reduction in drooling after BTX-A injections in children with sialorrhoea,[15] but study protocols vary with respect to the sample size, glands injected, dose of BTX-A, use of ultrasound-guidance, and follow up. The International Consensus Statement includes several recommendations that would clarify a protocol, including further research into the use of repeated injections.[16]

Our prospective study is one of a handful that have examined the effect of repeated BTX-A injections, and patients

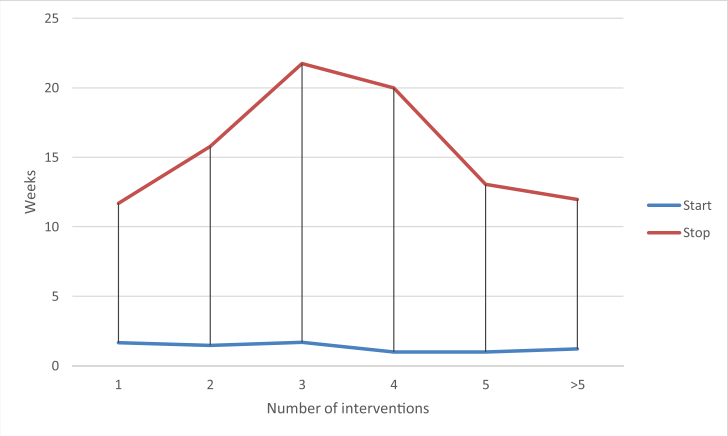

Fig. 2. Line graph to compare the therapeutic effect of BTX-A with the number of interventions.

who require surgical interventions. It is worth noting that a large proportion of our group (n = 21) had two or more injections, and our initial response rate of 91% compares favourably with other studies that reported injections into the both the parotid and submandibular glands.[3,15,17,18]

One of our primary aims was to find out whether BTX-A, when given at a constant dose, is still effective across a range of ages and weights. We found no significant differences in the effectiveness of the injections and the weight of our patients despite our fixed-dose regimen. In a similar study, Lungren et al also found no significant weight-adjusted dose response that was associated with effectiveness or complications.[19]

Another relative consistency was the therapeutic duration of BTX-A. The mean duration of effect with our relatively low-dose intervention was 3.5 months, which was similar to the findings in other studies that reported that the effect typically lasted between three and five months.[15,17] There is an established dose-response relation with higher doses that results in a more profound and prolonged reduction in drooling, but an increase in complications.[8,14,20] Despite multiple repeated interventions, our complication rate was relatively low with only one patient suffering from dysphagia soon after treatment. This common side effect has been reported in several studies and is probably caused by diffusion of the toxin into the surrounding tissues, leading to muscle weakness.[14] The effect can be limited by ultrasound-guided injections into the capsules of the parotid and submandibular glands, which are more accurate than blind injections, and may account for our low complication rate.[21]

While our data support the use of repeated BTX-A injections, it should be noted that only five patients had more than three, which limits the strength of the conclusions that can be drawn from any statistical analysis. In most cases the carers thought that drooling continued to reduce, which is consistent with the series described by Sillanpää et al who also reported good responses with repeated treatments (in most cases).[22]

Carers were also asked to compare the drooling at various intervals (1 month) and at subsequent follow-up appointments (mean 7.3 months). Although the greatest percentage reduction in the DFSS was at 1 month, a long-term reduction may be shown by a consistently lower score at subsequent follow ups. This could be the result of the impact of the toxin, which carers may have noticed for up to 12 months after the initial intervention. Previous studies, however, have hypothesised that repeated injections cause atrophy of the gland because of the prolonged chemical denervation of BTX, which results in a permanent reduction in drooling and improves the efficacy over the course of repeated treatments.[23]

Not all our patients improved, and close scrutiny of the results (Table 2) shows that it is difficult to work out the efficacy of the treatment for an individual. A reduction in the severity of drooling was not always associated with a reduction in frequency (n = 7) and, based on mean scores, seven patients either deteriorated further or showed no improvement after treatment.

There were two types of non-responders in our study: primary (no initial response), and secondary (initial response but failed to respond to the second intervention). A combination of factors may explain this discrepancy. First, our patients had ultrasound-guided injections into the submandibular and parotid glands to ensure that the drug was delivered accurately into the capsule. Despite the use of real-time imaging, however, there can still be a margin of error. So et al showed this in their cadaver study of ultrasound-guided BTX injections into the parotid (4.2%) and submandibular glands (8.3%), and this may partially account for the underwhelming response in both non-responder groups.[10] Secondly, a limitation of our study is that we did not assess whether BTX had previously been used in our patients to treat spasticity. Repeated injections of the toxin are associated with antibody-mediated resistance that results in a poor response, and 3%–10% of patients who are given large doses or repeated injections can develop antibodies.[15,17,24] To obtain an appreciable reduction in drooling, this group may therefore require a larger dose than our protocol has suggested.

The variation in protocols is also reflected in a systematic review Rodwell et al[14] who reported a median (range) dose of 25 (5–25) units/gland, which was greater than our protocol of 15 units/gland. Other technical factors that may influence outcomes, such as the number of sites injected/gland and which glands were injected (parotid or submandibular gland, or both), varied from study to study and made direct comparison difficult.[14]

It was encouraging to see that the confidence of the carers improved from 79% to 86% throughout the course of the study, and that most were satisfied with our service.

Limitations of the study include the subjective nature of the DFSS, VAS, and the drooling reduction score, which are prone to recall bias. Carers may have compared any reduction in drooling with the situation after the previous intervention rather than with the baseline before treatment began. One must also acknowledge the restrictions in the study period, which limited our follow up of patients who had repeated treatments. We also did not record whether patients had had BTX-A injections for other medical problems before enrolment into the study, and this could have had an impact on the efficacy of the treatment. A final caveat is the low response rate at the 1-month follow up (14/34 patients) which, despite its positive trend, limited our ability to predict the short-term effects of our regimen.

In conclusion, in children with sialorrhoea who are resistant to medical management, a repeated fixed-dosage protocol of BTX-A injections is safe and can confer positive short-term and long-term effects. Unfortunately, in a considerable number of patients there will be no benefit or this will be limited and, even in those who do respond, results remain temporary. Further research is therefore required to find out if repeated injections constitute a definitive treatment. In future we will consider whether higher doses are required in patients who respond only partially to repeated injections of the toxin.

Conflict of interest

We have no conflicts of interest.

Ethics statement/confirmation of patients' permission

This service evaluation project was formally registered within the Trust according to the local governance protocol. All patients' data were anonymised and stored on a secure server.

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