

Efficacy and Duration of Botulinum Toxin Treatment for Drooling in 131 Children

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Objective: To address the efficacy of botulinum toxin and the duration of its effect when used on a large scale for the treatment of drooling in children with neurological disorders.

Design: Prospective cohort study.

Setting: Academic multidisciplinary drooling clinic.

Patients: A total of 131 children diagnosed as having cerebral palsy or another nonprogressive neurological disorder and who also have moderate to severe drooling.

Intervention: Injection of botulinum toxin to the submandibular glands.

Main Outcome Measures: Direct observational drooling quotient (DQ) (0-100) and caretaker visual analog scale (VAS) scores (0-100).

Results: A clinically notable response was found in 46.6% of children, reflected in a significant mean reduction in DQ from a baseline of 29 to 15 after 2 months and 19 after 8 months ($P < .001$). The mean VAS score decreased from 80 at baseline to 53 after 2 months and increased to 66 after 8 months ($P < .001$). Kaplan-Meier analysis showed that patients who initially responded to treatment experienced relapse after a median of 22 weeks (interquartile range, 20-33 weeks).

Conclusions: Our study provides further support for botulinum toxin's efficacy for treatment of drooling in approximately half of patients for a median of 22 weeks. Further optimization of patient selection should be an area of attention in future studies.

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DROOLING IS A COMMON problem for children with neurological disorders. Recent estimates suggest a prevalence of nearly 60% in children in special care school, of which 33% could be classified as severe.¹ Drooling in these children is usually caused by a combination of low oral sensitivity, infrequent swallowing, poor posture and mental ability, and dysfunctional oral motor control leading to excessive pooling of saliva in the anterior oral cavity and consequently to unintentional saliva loss.^{2,3} Hypersalivation might only be an issue in children with dyskinesia as a result of hyperkinetic oral movements.⁴

The morbidity associated with sialorrhea has long been established in the literature.⁵⁻⁸ Depending on the associated neurological disorder, cognitive abilities, and oral motor function, affected children may experience anything from stigmatization and social neglect to numerous daily clothing changes, perioral dermatitis, aspiration pneumonia, or even dehydration. The management of drooling has long been a matter of debate. Speech therapy and be-

havioral therapy have been proposed, but our clinical experience suggests that this is only useful in children with sufficient cognitive abilities to train.⁹ Treatment with systemic anticholinergics appears to be effective, but these drugs are associated with notable adverse effects.¹⁰ Various surgical techniques have been reported to be highly effective, but owing to their invasive and often irreversible nature, other treatment techniques should be attempted first.

Intraglandular botulinum toxin, therefore, offered a promising treatment option when first suggested a decade ago.¹¹ Its localized nature and strong anticholinergic properties offered the potential to reduce drooling without the invasiveness of surgery. The intervention was subsequently demonstrated to be effective in a large number of studies, with most authors finding a clinically significant reduction in unwanted saliva loss in 33% to 64% of patients for approximately 2 to 6 months.¹² Botulinum toxin has been in use in our multidisciplinary drooling clinic since 1999. Our group has previously reported our initial results elsewhere.¹³⁻¹⁵ Our present aim is to report on the efficacy and

Table 1. Study Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Nonprogressive congenital neurological disease	Known hypersensitivity to botulinum toxin or any part of the formulation
Severe drooling, TDS score $\geq 3^a$	Missing baseline measurement, or missing >1 follow-up measurement
Conservative measures have not led to notable reduction in drooling, or are not feasible, eg, owing to low patient developmental level	Known use of other agents that influence drooling during the treatment Progressive disease

Abbreviation: TDS, Teacher Drooling Scale.¹⁶

^aA TDS of 3 corresponds with "occasional drooling, intermittent throughout the day."

duration of effect of botulinum toxin when used on a larger scale in clinical practice.

METHODS

PARTICIPANTS

Children eligible for inclusion were diagnosed as having cerebral palsy or another nonprogressive neurological disorder and were seen in our multidisciplinary drooling clinic for moderate to severe drooling. For each patient, conservative measures had not had sufficient effect or were not feasible, and injection of botulinum toxin to the submandibular glands was recommended as treatment. Full inclusion and exclusion criteria, including Teacher Drooling Scale¹⁶ score, are listed in **Table 1**.

STUDY DESIGN

Patients were enrolled consecutively between January 2000 and July 2008. Assessment of the severity of drooling took place under standardized conditions before treatment and 8 and 32 weeks after treatment. This allowed for a within-subjects design in which the patient's baseline condition was used as a reference to evaluate the effects of injection over time.

PROCEDURES

For the injection of botulinum toxin, children were under general anesthesia. A single dose of botulinum toxin type A (Botox; Allergan, Nieuwegein, the Netherlands), reconstituted with 0.9% sodium chloride, was then injected into the submandibular glands using a 25-gauge needle and a 1-mL syringe. The 1-mL volume was chosen to allow the dose to be fractionated over at least 3 sites in the gland while minimizing the risk of diffusion into surrounding tissues. We used 15 U of botulinum toxin per gland for children weighing less than 15 kg, 20 U/gland for children weighing between 15 kg and 25 kg, and 25 U/gland for children weighing more than 25 kg. During injection, the dose was fractionated over at least 3 sites in the gland under ultrasonographic guidance. The sublingual glands and parotid glands were not treated.

OUTCOME MEASURES

The drooling quotient (DQ), a validated, direct-observational semiquantitative method to assess the severity of drooling served as the primary outcome measure for both efficacy and duration of effect.¹⁴ The DQ was defined as the percentage of time

the patient drooled and was measured by 1 of 2 specially trained speech language therapists. During two 10-minute sessions (one while the patient was concentrating and the other while the patient was distracted), the absence or presence of new saliva on the lip was recorded every 15 seconds for a total of 40 observations per session. Patients were evaluated in the morning, at least 1 hour after a meal, while they were awake and sitting upright. *Response to treatment* was defined as a 50% reduction in DQ from the baseline value.

A caretaker visual analog scale (VAS) score reflecting the severity of drooling over the previous 2 weeks served as secondary outcome measure. Caretakers marked the extent of drooling on a 10-cm line following specific instruction. The VAS score was obtained by measuring the position of the mark in millimeters from the right end of the scale on a scale from 0 to 100, with 100 corresponding to severe drooling. A reduction of 2 SDs from the baseline VAS score was considered clinically significant.

Finally, qualitative assessments were made throughout the study of oral hygiene (including xerostomia), saliva viscosity, feeding behavior, and speech.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS software, version 16.0.2.1 for Mac OS X (SPSS Inc, Chicago, Illinois). For analysis of the DQ and VAS score, we used descriptive statistics; conducted paired *t* tests to assess differences of paired observations; performed independent *t* tests and linear regression to compare groups; and performed a multivariate analysis of variance with a repeated measures design to evaluate the treatment response pattern over time, using a within-subjects design with the measurement moments as the variables. Missing follow-up data were adjusted in 2 ways: (1) by carrying the last observation forward (CLOF) and (2) through a worst-case scenario (WCS). In the CLOF procedure, missing data were replaced with the last previous observation; in the WCS procedure they were replaced by baseline values, thus introducing a bias toward the null. The outcomes of both approaches are presented herein.

Analysis of the duration of the effect of botulinum toxin injection was accomplished by observing patients who were classified as responders beginning 8 weeks after intervention and performing a time-to-event (Kaplan-Meier) analysis until relapse occurred. The interval between the last known date of success and the end date was halved to compensate for the gradual loss of effect associated with botulinum toxin. All tests of significance were 2 sided, and $P \leq .05$ was considered statistically significant.

RESULTS

A total of 133 children were initially included. One was subsequently excluded because of a missing baseline assessment, and another for a complete lack of follow-up data. This left 131 children suitable for analysis, 77 boys and 54 girls. The mean (SD) age at the time of treatment in this group was 10.9 (4.7) years (age range, 3-27 years). Most of the patients were diagnosed as having cerebral palsy (90.1%), while the others had psychomotor retardation of unknown origin. Over half of the children had a Gross Motor Function Classification System score of 4 or higher, indicating that they relied on a wheelchair for mobility. A total of 41.2% of them had well-controlled epilepsy, and another 14.5% had intractable epilepsy.

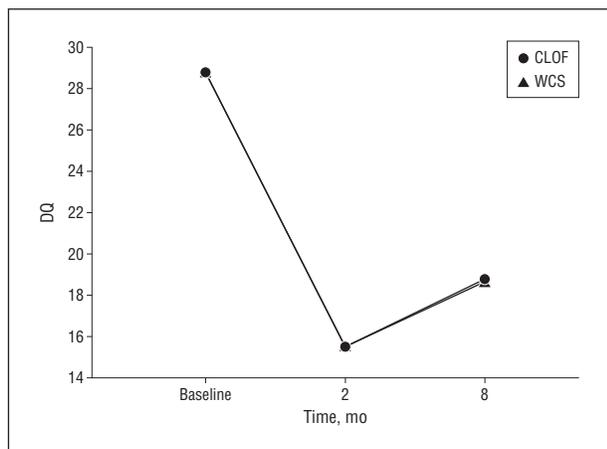


Figure 1. Mean direct observational drooling quotient (DQ) for the study patients (n=131). From a mean baseline value of 28.7, the mean DQ showed a significant reduction to 15.5 after 2 months and 18.7 after 8 months ($P < .001$). CLOF indicates carry last observation forward; WCS, worst-case scenario.

PRIMARY OUTCOMES

The follow-up rate at the 2-month interval (median interval, 8 weeks; interquartile range [IQR], 8-9 weeks) was 97.8%, and at the 8-month interval (median interval, 32 weeks; IQR, 31-34 weeks) it was 94.0%. No evidence was found of selective loss of follow-up.

Analysis of the DQ was first performed on the data adjusted by CLOF. Repeated measures analysis showed a highly significant reduction (Hotelling Trace $F = 38\,360$, $P < .001$), depicted in **Figure 1**. At the first follow-up, the mean DQ had fallen from a baseline value of 28.8 to 15.5, a change of -13.3 ($P < .001$). Sixty-one patients experience a 50% reduction in DQ from baseline and so were considered “responders” by our definition. Although follow-up after 8 months showed the beginning of a return to baseline, there was still a significant difference compared with the baseline assessment (-10.0) ($P < .001$). As a result of the high follow-up rate, WCS analysis did not yield notably different results ($F = 38\,878$, $P < .001$). Patient sex ($P = .10$), neurological score ($P = .07$), or age ($P = .32$) did not significantly influence outcome.

Detailed time-to-event analysis was subsequently performed for the 61 responders at the 2-month follow-up to investigate the duration of the effect provided by botulinum toxin. *Disease-free survival* was defined as the time the DQ remained below 50% of baseline values, and no repeated intervention was indicated or performed. Kaplan-Meier analysis showed a median duration of effect of 150 days (22 weeks) (**Figure 2**). An IQR of 138 to 235 days (20-34 weeks) indicated that 75% of patients who initially responded well to therapy stopped demonstrating a clinically significant effect before 8 months after injection. Four patients were lost to follow-up before relapse could be established (right-censored observations). At the last observation, these patients still experienced an ongoing effect, and the duration of effect in these cases is thus not known.

SECONDARY OUTCOMES

For 3 patients, VAS scores could not be analyzed owing to a missing baseline score. Analysis of the remaining 128

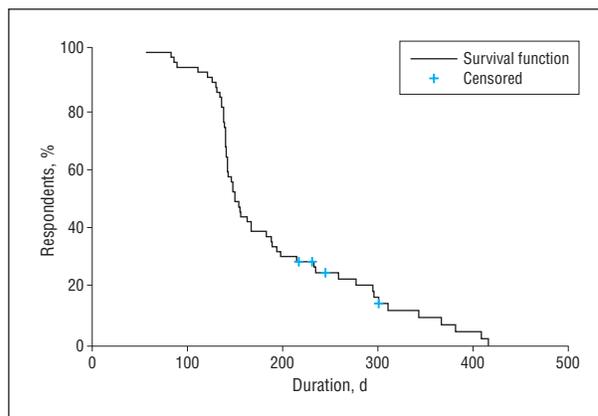


Figure 2. Duration of botulinum toxin effect. Kaplan-Meier analysis of longevity of botulinum toxin injection effect in patients who showed a response to treatment after 8 weeks (n=61). The median duration was 150 days; interquartile range, 138 to 235 days.

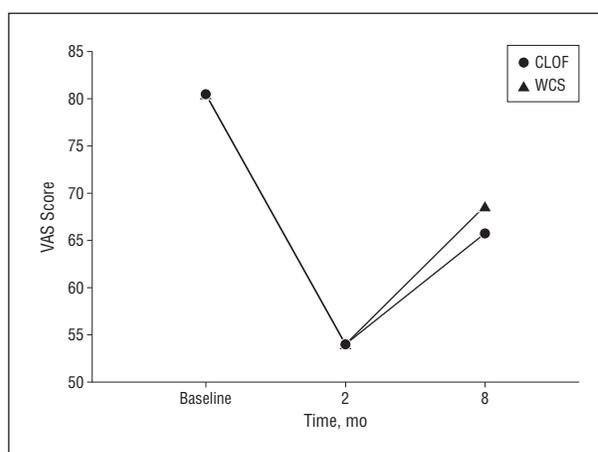


Figure 3. Mean visual analog scale (VAS) scores for the study patients (n=128). From a mean baseline value of 80.4, the VAS score fell to 53.9 after 2 months ($P < .001$). Although it had increased by 8 months, there was still a significant effect compared with baseline (CLOF, 65.7; WCS, 68.7) ($P < .001$). CLOF indicates carry last observation forward; WCS, worst-case scenario.

children showed a significant pattern similar to the DQ ($F = 58\,804$, $P < .001$), which is depicted in **Figure 3**. After 2 months, the mean VAS score had fallen from a baseline value of 80.4 to 53.9 ($P < .001$). After 8 months, the VAS score had risen to 65.7 ($P < .001$) (**Table 2**). Although there were more missing VAS score values (6 after 2 months, 20 after 8 months) than DQs, no meaningful differences were found between the CLOF and WCS analyses; only the 8-month score was slightly higher in the WCS setup (68.8). Response rates, defined as a reduction of 2 SD from the baseline score, were 51.0% after 2 months and 26.0% after 8 months.

Although injections were usually well tolerated, there were several minor adverse effects in this series. Changes in the viscosity of saliva were perhaps the most common side effect of treatment: 54 children experienced thickening of saliva at some point as noticed by parents or detected by clinicians at follow-up (41.2%). Interestingly, a reduction in saliva viscosity was reported 16 times (12.2%). Transient difficulty in swallowing was reported by 4 patients (3.1%), presumably mostly as a result of altered sa-

Table 2. Mean Differences Between Baseline and Follow-up Measurements^a

Observation Period	DQ (95% CI)		VAS (95% CI)	
	CLOF	WCS	CLOF	WCS
Baseline to 2 months	-13.3 (-16.3 to -10.3)	-13.3 (-16.3 to -10.3)	-26.5 (-31.3 to -21.6)	-26.5 (-31.3 to -21.6)
Baseline to 8 months	-10.0 (-13.0 to -7.0)	-10.1 (-13.1 to -7.2)	-14.7 (-19.1 to -10.3)	-11.6 (-15.6 to -7.7)
Two months to 8 months	3.3 (0.8 to 5.7)	3.2 (0.7 to 5.7)	11.8 (7.3 to 16.3)	14.8 (9.9 to 19.7)

Abbreviations: CI, confidence interval; CLOF, carry last observation forward; DQ, drooling quotient; VAS, visual analog scale; WCS, worst-case scenario.

^aBased on paired-samples *t* tests, 2-sided *P* ≤ .05.

liva consistency, although diffusion of toxin into surrounding tissue cannot be excluded as a cause. Eight children showed temporarily deteriorated feeding behavior (6.1%), while 9 patients showed improved feeding (6.9%). Two patients reported xerostomia after 2 months (1.7%), which had resolved after 8 months.

Secondary beneficial effects following injection included improved oral hygiene (reduced perioral dermatitis or reduction in halitosis) in 4 patients (3.1%) and improved speech in another 4 patients. These effects generally disappeared after 8 months.

COMMENT

To our knowledge, this is the largest described series of patients treated for drooling with intraglandular botulinum toxin. In these 131 patients, we found an objective and subjective response rate of approximately 50%, similar to that found in smaller studies. Responders benefited from injection for a median of 22 weeks. After 33 weeks, 25% of initial responders (11.3% of the entire population) still showed a clinically significant response to the toxin, with a handful of patients experiencing continued drooling relief after 1 year.

Morbidity associated with the procedure was limited. Changes in the viscosity of saliva were reported very frequently but rarely led to severe problems, perhaps partially as a result of the dietary advice given to caretakers to provide only food that was easily mashed or melted for several days following injection. Only 2 patients reported xerostomia, indicating that saliva production from the sublingual, parotid, and minor salivary glands was usually sufficient to maintain a physiologically moist oral cavity.

No predictors for successful treatment were found in this series, although it should be noted that this was not a primary objective of the present study. Motor function was expected to correlate with outcome, but this was not confirmed by these data. A larger sample might be required to detect this; alternatively, other factors might influence response to therapy, such as posture, oral motor function, or diet, data for which were not available for this study. It thus remains unclear why some patients benefit so much more or so much longer from botulinum toxin injection than others. As many patients are currently treated without experiencing meaningful benefits, more information on factors influencing outcome and duration of effect would be very useful.

It should be noted that injections in our study were limited to the submandibular glands; these are respon-

sible for 70% of resting saliva production. The parotids mainly secrete during mastication. However, combined injections to the submandibular and parotid glands appear to be used more frequently.¹⁷⁻¹⁹ Our clinical experience hints that combined injections could indeed be slightly more effective than isolated submandibular injections, but there is currently little scientifically sound evidence to support or disprove this impression.

Another important issue surrounding the application of botulinum toxin is still the effect of repeated injections. Prolonged denervation of salivary glands induces atrophy of the gland,²⁰ and it has been hypothesized that chemical denervation via repeated botulinum toxin injection could bring about a similar effect and thus lead to a permanent reduction in drooling.¹⁴ On the other hand, a recent report has described secondary nonresponse to botulinum toxin type B following repeated injection, implying that there may be a limit to the number of effective treatments with botulinum toxin for some patients.²¹ Systematic studies in this area, however, have yet to appear.

Until evidence for a cumulative effect appears, botulinum toxin should therefore be considered a temporary solution to relieve drooling, as the current study underscores. In our tertiary center, submandibular botulinum toxin is used as a first-line treatment for patients for whom oral motor training or behavioral therapy have failed or are not considered feasible. Renewed injections are considered on a case-by-case basis. Combined parotid and submandibular injections are generally reserved for patients with a severely inadequate swallowing mechanism and suspected aspiration or for patients who have not sufficiently responded to submandibular injections. We prefer not to give combined injections to children who are fed orally because the diminished food bolus lubrication might pose a risk in children for whom ample saliva is just barely enough. Reducing salivary flow too much in such cases could potentially impair oral feeding. Surgery is advised if (1) the patient has reached an age when it is unlikely that further development will cure the drooling (usually from approximately 12 years), (2) drooling persists despite repeated botulinum toxin injection, or (3) patients express a desire for a permanently effective solution. We believe that systemic anticholinergic therapy should be prescribed with great caution because (1) it carries the risk of serious adverse effects and (2) the less risky localized anticholinergic therapy via botulinum toxin can be quite effective.

Although the observational nature of our study makes it difficult to make definitive statements about the mag-

nitude of botulinum toxin's effect, our results provide further support for the clinical efficacy of botulinum toxin for drooling in patients with nonprogressive neurological disease. Furthermore, they indicate that most patients who initially respond well to injection can expect an effect to last between 19 and 33 weeks. Although the 46.6% success rate might appear low, its safety and efficacy make botulinum toxin a useful first-line invasive treatment if conservative measures have failed. Improved patient selection could perhaps increase the response rate. This, together with the effectiveness of repeated injection and combined parotid/submandibular injection should therefore be areas of specific attention in future studies.

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Author Contributions: Dr Scheffer had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. **Study concept and design:** Scheffer, Erasmus, van Limbeek, Jongerius, and van den Hoogen. **Acquisition of data:** Scheffer, Erasmus, and van Hulst. **Analysis and interpretation of data:** Scheffer, van Limbeek, Jongerius, and van den Hoogen. **Drafting of the manuscript:** Scheffer, van Limbeek, Jongerius, and van den Hoogen. **Critical revision of the manuscript for important intellectual content:** Scheffer, Erasmus, van Hulst, van Limbeek, Jongerius, and van den Hoogen. **Statistical analysis:** Scheffer, van Limbeek, and van den Hoogen. **Administrative, technical, and material support:** Erasmus and van Hulst. **Study supervision:** Scheffer, Erasmus, van Limbeek, Jongerius, and van den Hoogen. **Financial Disclosure:** None reported.

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