Radboud Repository

Radboud University Nijmegen

PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/174287

Please be advised that this information was generated on 2020-11-24 and may be subject to change.

Negative effects of submandibular botulinum neurotoxin A injections on oral motor function in children with drooling due to central nervous system disorders

KAREN VAN HULST[1] | CARLYN V KOUWENBERG[2] | PIETER H JONGERIUS[3] | TON FEUTH[4] | FRANCISCUS J A VAN DEN HOOGEN[5] | ALEXANDER C H GEURTS[1] | CORRIE E ERASMUS[2]

1 Department of Rehabilitation, Donders Centre for Neuroscience, Radboud University Medical Centre, Nijmegen; **2** Department of Neurology, Donders Centre for Neuroscience, Radboud University Medical Centre, Nijmegen; **3** Department of Rehabilitation, Rehabilitation Centre Sint Maartenskliniek, Nijmegen; **4** Department of Health Evidence, Radboud University Medical Centre, Nijmegen; **5** Department of Otorhinolaryngology, Radboud University Medical Centre, Nijmegen, the Netherlands.

Correspondence to Karen van Hulst at Department of Rehabilitation, Radboud University Medical Centre, PO Box 9101, local address 818, 6500 HB Nijmegen, the Netherlands.
E-mail: karen.vanhulst@radboudumc.nl

This article is commented on by Reddihough on pages 460–461 of this issue.

PUBLICATION DATA
Accepted for publication 29th September 2016.
Published online 30th November 2016.

ABBREVIATIONS

BoNT-A	Botulinum neurotoxin A
SLT	Speech language therapist

AIM The aims of this study were: (1) to determine the incidence and nature of adverse effects on oral motor function after first injections of botulinum neurotoxin A (BoNT-A) in submandibular glands for excessive drooling in children with central nervous system disorders; and (2) to identify independent predictors of these adverse effects.
METHOD A cohort study involved 209 children (123 males, 86 females, aged 4–27y, median 8y 4mo), who received submandibular BoNT-A injections for drooling. Adverse effects were categorized into swallowing, eating, drinking, articulation, and other problems. Univariable logistic regression was used to study differences in patients with and without adverse effects. Possible predictors were identified using multivariable logistic regression.
RESULTS Transient adverse effects occurred in 33% of the 209 BoNT-A treatments. Almost 80% of these were mild, versus 8.7% severe. Approximately 54% of the adverse effects spontaneously resolved within 4 weeks; 3% still existed after 32 weeks. A diagnosis of cerebral palsy, higher range of BoNT-A dosage, and a pre-treatment drooling quotient <18% were found to be independent predictors of adverse effects.
INTERPRETATION Before using submandibular BoNT-A injections for drooling, potential adverse effects should be discussed. Oral motor function needs to be monitored, because existing dysphagia may be worsened. The identified clinical predictors could be helpful to optimize patient selection.

Treatment with botulinum neurotoxin (BoNT) in the salivary glands is a widely accepted effective intervention for drooling in children with central nervous system (CNS) disorders. When injected into the salivary glands, BoNT inhibits the acetylcholine release at the terminal nerve endings, decreasing the secretion of saliva and diminishes drooling in the majority of patients.[1]

The main group of children with neurological impairments treated with BoNT injections are children with cerebral palsy (CP), a vulnerable group with a spectrum of oral motor problems (estimated 40% drooling prevalence).[2–4] Drooling has a serious impact on the children's social interaction, self-esteem, and health.[5] The effectiveness of salivary gland BoNT has been studied extensively, although the debate about which glands should be injected is still going on. Several studies demonstrated that, after BoNT, drooling is significantly reduced. In Scheffer's study a clinically notable response was found in 46.6% of children.[6] The duration of this effect was approximately 2 to 6 months (median 24wks).[6–8] In most of these studies, botulinum neurotoxin A (BoNT-A) was used.[9]

Considering the increasing use of BoNT for drooling, studies to identify possible risk factors for adverse effects on oral motor functions before treatment are urgently needed.[10] Post-intervention assessments showed that adverse effects on oral motor functions with a potential negative effect on swallowing occurred from 0%[11–13] up to 17.8%[6] of the cases after submandibular gland injections, and up to 33%[14] of the cases after combined submandibular/parotid gland injections. To date no major complications were identified after submandibular injections.

Knowledge of the incidence, nature, and risk factors of adverse effects will help to predict which children with

© 2016 The Authors. *Developmental Medicine & Child Neurology* published by John Wiley & Sons Ltd on behalf of Mac Keith Press. DOI: 10.1111/dmcn.13333
This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

CNS disorders will positively qualify for BoNT to ameliorate excessive drooling.

The objectives of this study were: (1) to determine what adverse effects on oral motor function occur up to 8 months after the first BoNT-A injections in the submandibular glands; (2) to describe the incidence and course of these adverse effects; and (3) to identify independent predictors for adverse effects on oral motor function.

What this paper adds

- Transient adverse effects of submandibular botulinum neurotoxin A (BoNT-A) injections on oral motor function occur in 33% of all cases.
- Predictors of the occurrence of adverse effects of BoNT-A treatment are diagnosis of cerebral palsy, higher dosage of BoNT-A, and a pre-treatment drooling quotient <18%.
- Although BoNT is a valuable treatment for drooling, careful evaluation before treatment and aftercare are crucial.

METHOD

Design and patient selection

In this cohort study, 209 children (123 males, 86 females; median age at inclusion 8y 4mo, aged 4–27y) participated. Inclusion criteria were: (1) first treatment with BoNT-A injections in the submandibular glands in the period between January 2002 and May 2013; (2) moderate to severe drooling with a score of three or higher on the Teacher Drooling Scale (occasional drooling, intermittent, all day); (3) minimum age of 4 years; (4) a minimum of two measurements representing baseline and at least one follow up; and (5) no previous surgical procedure for saliva control. Informed consent for BoNT-A treatment was obtained from the child's legal representative(s). Parents or caregivers were informed about the consequences and the expectations of the treatment before the injections. All injections were administered as part of regular care.

Patient characteristics

All children were assessed before treatment by members of the multidisciplinary saliva control team of the Radboud University Medical Centre. A medical assessment was performed by the pediatric neurologist and the ear, nose, and throat (ENT) specialist. Two specifically trained speech and language therapists (SLTs) carried out a social evaluation and an oromotor assessment. The quantity of drooling and the impact of the intervention on the severity of drooling were measured with objective and subjective scales at three different moments: before (t1), 8 weeks (t2), and 32 weeks after the injections (t3). The severity of drooling was quantified with the modified drooling quotient.[15] A caretaker visual analogue scale score (range 0–10) reflected the severity of drooling, with 0 indicating 'no drooling' and 10 indicating very severe drooling.[5] Based on direct SLT observations and parental reports, the viscosity of saliva was judged before and after BoNT-A (more serous/more mucus/unchanged).

Treatment characteristics

Intraglandular injections of BoNT-A (Botox; Allergan, Nieuwegein, the Netherlands) were performed by the team's pediatric rehabilitation specialist under ultrasound guidance and general anesthesia. Treatment consisted of bilateral injections in the submandibular glands. Botox was diluted in saline 0.9% (25U/mL). Using a Spinocan needle, 1ml was divided over two or three sites throughout the gland. Occasionally, slightly more BoNT-A was injected to attain optimal spread, up to a maximum of 30U Botox per gland. For every child the applied dosage of BoNT-A per gland was noted in the medical records. The clinically relevant response at t2 to BoNT-A treatment was defined as ≥50% reduction in drooling quotient and/or a reduction of 2 standard deviations from the baseline visual analogue score to obtain a combined objective and subjective outcome.[6]

Adverse effects

If the caregivers noticed any post-treatment change in oral motor function during the first 8 weeks, they were encouraged to contact the SLT for advice and, if needed, they were invited for an additional visit at the outpatient clinic. Adverse effects were elicited as a part of our usual care during each follow up moment at 8 weeks and 32 weeks through a semi-structured interview. During the SLT measurements at t2 and t3, we specifically asked for any probable adverse effect or change in health condition. Negative oral motor problems were recorded and categorized according to the International Classification of Functioning, Disability and Heath, Children and Youth version (ICF-CY). Five subdomains remained: (1) saliva swallowing=reported changes in saliva viscosity, increased choking on saliva, and/or reported discomfort during swallowing saliva; (2) eating=reported discomfort during eating (coughing, gagging), deteriorated feeding pattern; (3) drinking=reported discomfort during drinking (coughing, choking, dyspnoea); (4) articulation=reported deteriorated speech; (5) other problem=reported other discomfort, as sore throat, dry mouth/lips, and teeth grinding. Adverse effects were subdivided into three categories: mild, moderate, and severe (definitions in Table II). The predefined outcome definition was dichotomous: adverse effects occurrence 'yes' versus 'no'.

Statistics

Descriptive statistics were used to determine general characteristics of the children and allocated treatments, and the incidence and occurrence of the adverse effects. Medians and minimal/maximal values were calculated for continuous variables. The association between post BoNT-A saliva viscosity (more concentrated mucus saliva) and the appearance of adverse effects was calculated by a chi-squared test, as well as the relationship between the occurrence of adverse effects and the response to BoNT-A injections. Univariable logistic regression was used to study associations between patient characteristics, the BoNT-A dosage, and the occurrence of adverse effects. The adverse effects prevalence (*n*) and the crude odds ratio (OR) with 95%

confidence intervals (CI) are presented. Potential predictors of adverse effects incorporated in the model were based on biological plausibility and a previous publication of the drooling quotient.[15] Model selection was done using backward stepwise elimination with p=0.100 levels of removal. Results with two-tailed p-values <0.050 were considered significant. The adjusted ORs with 95% CI of the final model were calculated. The area under the curve (AUC) of the receiver operating characteristic (ROC) curve was used as a measure of predictive discrimination. Missing descriptive values were considered as missing completely at random (MCAR). To calculate treatment responses, missing values of drooling quotient and visual analogue scores were imputed according to the worst-case scenario: missing data were replaced with the last previous observation or replaced by baseline values. Statistical analyses were carried out using SPSS 20.0 for Windows (IBM Corp., Armonk, NY, USA).

RESULTS

Patient and treatment characteristics

Our data set of 209 children contained 130 children with CP (62.2%), whereas 78 children (37.3%) were classified as non-CP (e.g. epileptic encephalopathy or neurogenetic syndromes) (Table I). The disease course was complicated by intractable seizures in 18 children (8.6%). All children had received bilateral submandibular BoNT-A injections, 182 (87.1%) with a dosage of 25U, 16 (7.7%) had received <25U per gland, and 8 (3.8%) had received more than 25U per gland. Most children (n=136; 65%) were classified as responders, whereas 73 (35%) were considered to be non-responders at t2.

Adverse effects

The incidence and characteristics of the adverse effects are listed in Table II together with the advices and interventions given post treatment. Adverse effects were recorded in 69 (33%) of the children. Of the 69 children with adverse effects, 22 children (31.9%) experienced saliva swallowing, 51 (73.9%) eating, 22 (31.9%) drinking, 4 (5.8%) articulation, and 15 (21.7%) other problems. In 37 children (53.6%) with any type of adverse effects, an isolated oral motor problem occurred. Simultaneous problems co-occurred in two domains in 23 (33.3%), in three domains in 5 (7.2%), and in four domains in four children (5.8%). Severe adverse effects appeared to be related to the occurrence of multiple problems in one individual at the same time. Of the six children with severe adverse effects, only one child reported one problem, whereas one child experienced two problems, two children three problems, and two children four problems at the same time. In 54 (78.3%) the onset of the adverse effects occurred within 1 week after treatment, while complete disappearance occurred in 37 children (53.6%) before the end of the fourth week post treatment. Two children experienced adverse effects longer than 8 months. The severity of the adverse effects was mild in 55 (79.7%) and no post-treatment intervention was needed in 50 of these children

Table I: Characteristics of study population at baseline (t1) (n=209)

Patient characteristics	n (%)
Sex	
Male	123 (58.9)
Female	86 (41.1)
Age at inclusion	
Median	8.4 (4.1–27.8)[a]
Diagnosis	
CP	130 (62.2)
Non-CP[b]	78 (37.3)
Unknown	1 (0.5)
Disease course[c]	
Complicated	18 (8.6)
Non-complicated	190 (90.9)
Unknown	1 (0.5)
Mental ability	
Developmental age <4y	131 (62.7)
Developmental age >4y	78 (37.3)
Degree of mobility	
Ambulant	104 (49.8)
Non-ambulant	105 (50.2)
Cause of drooling	
Low cognitive awareness	25 (12)
Impaired oral phase of swallowing	126 (60.2)
Impaired oropharyngeal phase of swallowing	58 (27.8)
Nutrition intake	
Tube/tube and oral	34 (16.3)
Oral	175 (83.7)
Choking on saliva	
Yes	59 (28.2)
No	145 (69.4)
Unknown	5 (2.4)
Choking on food	
Yes	96 (45.9)
No	109 (46.8)
Unknown	4 (1.9)
Choking on drinks	
Yes	107 (51.2)
No	99 (47.4)
Unknown	3 (1.4)
DQ	
Median	27.5 (0–100)[a]
Unknown	2 (1)
VAS	
Median	8 (3.4–10)
Unknown	2 (1)
Treatment characteristics:	
Dosage of BoNT-A per gland, n (%)	
Dosage<25U	16 (7.7)
Dosage=25U	182 (87.1)
Dosage>25U	8 (3.8)
Unknown	3 (1.4)
Saliva viscosity at t2, n (%)	
More serous	17 (8.1)
More mucus	76 (36.4)
Unchanged	76 (36.4)
Unknown	40 (19.1)
Treatment response,[d] n (%)	
Responder	136 (65.1)
Non-responder	73 (34.9)

[a]Data of age, DQ and VAS are presented as median (min/max). [b]Non CP: children with developmental disability mainly as part of a syndrome, genetic, metabolic or neurodegenerative disorder. [c]Complicated: in case of a progressive disease or if something unexpected happened (e.g. uncontrolled epilepsy), Non-complicated: when the course did not deviate from expected. [d]Treatment response: treatment with BoNT-A was defined as effective and clinically useful if ≥50% reduction in DQ was found and/or if a reduction of ≥3.86 (2SD) of the VAS score (0–10) occurred at t2 compared to t1. CP, cerebral palsy; y, year; BoNT-A, Botulinum neurotoxin A; t1, baseline; U, unit; DQ, drooling quotient; VAS, visual analogue scale.

Table II: Incidence and characteristics of adverse effects of first botulinum neurotoxin A (BoNT-A) injections in the submandibular glands as well as advices/interventions given post treatment (*n*=209)

	n (%)
A. Incidence of adverse effects	
Adverse effects	
Yes	69 (33.0)
No	140 (67.0)
B. Characteristics of adverse effects (*n*=69)	
Severity of problem[a]	
Mild	55 (79.7)
Moderate	7 (10.1)
Severe	6 (8.7)
Not specified	1 (1.5)
Oral motor problem[b]	
Saliva swallowing problems	22 (31.9)
Eating problems	51 (73.9)
Drinking problems	22 (31.9)
Articulation problems	4 (5.8)
Other	15 (21.7)
Number of co-occurring oral motor problems	
1	37 (53.6)
2	23 (11.0)
3	5 (2.4)
4	4 (1.9)
Time of problem onset	
<1wk	54 (78.3)
1–8wks	5 (7.2)
Unknown	10 (14.5)
Duration of problem	
<1wk	12 (17.4)
1–4wks	25 (36.2)
4–8wks	6 (8.7)
8–32wks	7 (10.2)
>32wks	2 (2.9)
Unknown	17 (24.6)
C. Post treatment advices/interventions	
Interventions	
None	50 (72.5)
Phone consultancy	11 (15.9)
Additional outpatient visit	3 (4.3)
Hospital admission	4 (5.8)
Other[c]	1 (1.5)
Advices	
Start (or increase) of tube feeding	2 (2.9)
Adapt feeding/consistency	9 (13.0)
Medication	1 (1.5)
Other	5 (7.2)
None	50 (72.5)
Unknown	2 (2.9)

[a]Mild: short transient changes in saliva swallowing, eating, drinking, or articulation, not leading to changes in lifestyle or doctor visits. Moderate: transient changes in oral motor functions or losing weight, nearly always requiring consultation by a general practitioner. Severe: change in oral motor function requiring one or more days of hospitalization or substantial changes in feeding (e.g. tube feeding). [b]Multiple problems per child are possible. [c]Other: combination of advice or interventions.

(72.5%). Of the children who experienced severe adverse effects, 4 (5.8%) needed hospital admission or required a substantial change in feeding or a nasogastric tube feed for a few weeks (2.9%). Concerning the phone calls by SLTs and additional outpatient visits, advice involved medication, the adaptation of the food consistency, supportive care, and explanation of the problem (21.7% of the cases).

In 76 of the 209 cases (36.4%) saliva became more mucus at t2. Increased viscosity of saliva was positively related to the occurrence of an adverse effect (X^2 [1, *n*=209]=11.5, *p*=0.001). No relation was found between the occurrence of adverse effects and being a responder or non-responder to BoNT-A injections at t2 (X^2 [1, *n*=209]=0.42, *p*=0.521).

Prediction model

In Table III, crude ORs and adjusted ORs are given for the biologically plausible risk factors for any adverse effect. The ordinal category with the suspected lowest adverse effect chance was chosen as a reference. Statistically significant predictors of adverse effects were having a diagnosis of CP, higher dosage of BoNT-A, and a pre-treatment drooling quotient below 18%. When all other variables remained stable, children with CP were 3 times more likely to experience an adverse effect (OR: 3.08; 95% CI: 1.53–6.19) than other children. Compared to children injected with <25U Botox, treatment with a dosage of 25U Botox increased the odds of experiencing an adverse effect by a factor 5 (OR: 5.06; 95% CI: 1.07–23.84), whereas children injected with more than 25U Botox were eight times more likely to have an adverse effect (OR: 8.13; 95% CI: 1.02–64.96). Lastly, a pre-treatment drooling quotient <18% increased the odds (OR: 2.40; 95% CI: 1.18–4.88) of developing adverse effects compared with a pre-treatment drooling quotient ≥18%. The AUC of the ROC curve for the multivariable regression analysis was 67% (95% CI: 60–75%).

DISCUSSION

To our knowledge this series represents the largest cohort of children (*n*=209) who received BoNT-A injections exclusively in the submandibular glands. Moreover, our registration of adverse effects was based on a standardized face-to-face contact 8 weeks and 32 weeks post injections. From this study it can be concluded that adverse effects on oral motor functions occur in 33% of the children but, at the same time, that almost 80% of the adverse effects were 'mild' and 54% disappeared within 4 weeks after the injections. By categorizing the oral motor problems after BoNT-A in different domains, we found that eating problems were reported the most, followed by (saliva) swallowing and drinking problems. Only the group of children with moderate and severe adverse effects (*n*=13) needed advice and supervision of the SLT or physician. Considering the pharmacology of BoNT-A, two individuals exhibited unexplained adverse effects lasting longer than 32 weeks, as the normal (median) duration of BoNT efficacy for drooling is 22 weeks.[6]

In previous studies, the incidence of mild or moderate complications of submandibular BoNT injections in children ranged from 0% to 17.8%.[6,11–13] In the present study we found such complications in 29.7% of the cases, whereas severe adverse effects occurred in 2.9%. Because protocols differed between studies with respect to intervention and follow-up, we estimated the percentages of patients with complications per treatment. Most studies reported complications after combined BoNT injections into the parotid and submandibular glands, or after repeated salivary gland

Table III: Number of patients with and without adverse effects (AE+/−) and ORs and adjusted ORs with 95% confidence interval based on univariable and multivariable logistic regression analysis with AUC[a] respectively

Number of patients				
Characteristics	AE− (%) (*n*=140)	AE+ (%) (*n*=69)	OR (95% CI)	Adjusted OR (95% CI)
Sex				
Male	81 (57.9)	42 (60.9)	1.00 (reference)	–
Female	59 (42.1)	27 (39.1)	0.88 (0.49–1.59)	–
Developmental age				
<4y	91 (65.0)	40 (58.0)	1.35 (0.75–2.43)	–
≥4y	49 (35.0)	29 (42.0)	1.00 (reference)	–
Diagnosis				
Non CP	61 (43.9)	17 (24.6)	1.00 (reference)	1.00 (reference)
CP	78 (56.1)	52 (75.4)	2.39 (1.26–4.54)	3.08 (1.53–6.19)[b]
Unknown	1			
Degree of mobility				
Ambulant	75 (53.6)	29 (42.0)	1.00 (reference)	–
Non-ambulant	65 (46.4)	40 (58.0)	1.59 (0.89–2.85)	–
Injected dosage BoNT per gland				
<25U	14 (10.2)	2 (2.9)	1.00 (reference)	1.00 (reference)
25U	119 (86.9)	63 (91.3)	3.71 (0.82–16.82)	5.06 (1.07–23.84)[b]
>25U	4 (2.9)	4 (5.8)	7.00 (0.92–53.23)	8.13 (1.02–64.96)[b]
Unknown	3			
Nutrition intake				
Tube/tube and oral	25 (17.9)	9 (13.0)	1.00 (reference)	–
Oral	115 (82.1)	60 (87.0)	1.45 (0.64–3.30)	–
Choking on saliva (t1)				
No	98 (70.5)	47 (72.3)	1.00 (reference)	–
Yes	41 (29.5)	18 (27.7)	0.92 (0.48–1.76)	–
Unknown	1		4	
Choking on food (t1)				
No	77 (55.8)	32 (47.8)	1.00 (reference)	–
Yes	61 (44.2)	35 (52.2)	1.38 (0.77–2.48)	–
Unknown	2		2	
Choking on drinks (t1)				
No	67 (48.6)	32 (47.1)	1.00 (reference)	–
Yes	71 (51.4)	36 (52.9)	1.06 (0.59–1.90)	–
Unknown	2		1	
DQ (t1)				
DQ<18	87	52	1.94 (1.01–3.75)	2.40 (1.18–4.88)[b]
DQ≥18	52	16	1.00 (reference)	1.00 (reference)
Unknown	1	1		

[a]The area under the ROC curve for multivariable logistic regression analysis was 67% (95% CI: 60–75%). [b]Significant predictors of adverse effects based on multivariable logistic regression analysis. AE+, patients with adverse effects; AE−, patients without adverse effects; OR, odds ratio; –, variables not selected in the multivariable logistic regression analysis.

injections in the same individual.[14,16–18] Chan et al.[19] found 15.8% complications after combined injections with major complications in 4% of the cases. In a study by Khan et al., 15 of the 45 patients (33.3%) experienced at least one problem after combined injections. Major problems requiring intensive therapy and prolonged hospitalization occurred in 11.1% of the cases.[14] The adverse effect definition and strict follow-up protocol in our study may be the reason for the relatively high adverse effect percentages. However, it should be noted that some adverse effects in Chan et al.'s[19] study may not have been recognized because of possible recall bias (telephone survey response rate 51%). In conclusion we see fewer severe adverse effects (2.9%) after the two-gland method with isolated submandibular injections than after the four-gland method with combined parotid and submandibular gland injections (4–11.1% complications); this, as also indicated by Gok et al.,[13] would be the first choice in saliva control treatment when BoNT-A injections are considered in children.

Children with CNS disorders who are treated for drooling are vulnerable with regard to their oral motor abilities. In present study, 28.2 to 51.2% already showed dysphagia at baseline. After BoNT-A, the oral motor problems increased in 69 children (33%). As expected, a higher frequency of adverse effects occurred in children with oral feeding skills (87%). Our findings underline the recommendation by Reddihough et al.[1] to regularly contact the patient's caregivers in the weeks after BoNT injections to evaluate oral motor problems.

Authors mentioned two main causes for the deterioration of swallowing and/or speech. Higher salivary viscosity after BoNT-A injections may result in problems with intraoral processing of (solid) food.[20,21] Indeed, we found a significant association between increased salivary viscosity and the occurrence of adverse effects. Concerning oral motor function, the second potential cause of BoNT-related problems is the diffusion of the toxin outside the salivary gland leading to muscle weakness.[6,20] The

submental muscle group (SMG) plays an important part in normal swallowing.[22,23] After submandibular BoNT, diffusion into the SMG most likely results in muscle weakness and, as a consequence, the child may not properly control the swallowing process leading to oral dysfunction.

Up to now, it has been unknown which children with CNS disorders will experience adverse effects after BoNT treatment. We tried to discover potential risk factors and identified three clinically significant predictors of the occurrence of adverse effects: diagnosis of CP, higher BoNT-A dosage, and pre-treatment drooling quotient of <18%.

Children with CP were three times more likely to experience an adverse effect than other children. This finding may be attributed to the fact that, in children with CP, drooling is generally caused by an impaired oropharyngeal swallowing caused by poor oral muscle control.[3,16] In other children with CNS disorders drooling is usually less associated with motor control, but more commonly caused by less awareness and inability to recognize salivary spill.[17] We hypothesize that, in some children with CP, changes in the viscoelastic properties and the decreased salivary amount, or induced muscle weakness, cannot adequately be compensated by the oral motor system.

In the present study we had the opportunity to compare different dosages of BoNT per submandibular gland. Children treated with 25U and >25U Botox per gland were more at risk of an adverse effect (5 and 8 times higher risk respectively). Recently, Moller et al.[9] found no relationship between adverse effects and the administered dose or injection method of BoNT-A. Some authors have speculated whether a high volume of liquid or a slower speed of delivery may affect the likelihood of dispersal into surrounding tissues.[18] Currently, the most effective dilution of BoNT and the number of injection sites within the gland are still under debate. Normally, the amount of fluid injected raises the intraglandular pressure and, theoretically, leakage of the drug might occur. Tighe et al.[24] also recently reported dysphagia after BoNT-A extravasation from the glandular puncture site, possibly depending on the injected volume.

At baseline, children who had a drooling quotient <18 (i.e. mild drooling) were 2.4 times more likely to develop an adverse effect. The drooling quotient is a reliable objective measure of unintentional loss of saliva from the mouth. In a previous study by our team, we concluded that children with a drooling quotient <18 may be eligible for a more conservative intervention, such as oral sensorimotor training. In cases when those children receive BoNT, because of a failure of the oral motor training and the high impact of the drooling, the mouth could possibly become dry, interfering with mastication. On the other hand, the drooling quotient is a measurement for anterior (visible) drooling and children with a low drooling quotient might be sensitive to posterior drooling, making them more vulnerable to adverse effects – i.e. those children lack the strength to process the thickened saliva making them prone to saliva swallowing problems. We argue that this cut-off threshold should not be applied as the only variable to indicate an invasive treatment. The use of subjective measurements of the severity and impact of drooling on the child and parents should also be encouraged.[15]

Interestingly, we could not find a relation between the occurrence of an adverse effect and being a responder or not. Thus, we are convinced that it is justified to treat children with CNS disorders for chronic drooling because the majority of the adverse effects are mild and will improve within a few weeks in most of the cases.

A limitation of our study is that we focused on a limited set of factors that might influence the occurrence of adverse effects. There may be other risk factors of importance such as the use and/or change of oral medication during/after BoNT treatment. In addition, we did not document any concurrent BoNT injections into the skeletal muscles to treat spasticity. Indeed, disturbances of swallowing and speech have been reported after multilevel intramuscular injections,[25,26] because the total amount of BoNT in the body is substantially increased after combined intraglandular and intramuscular injections. Thus, clinicians should be aware of the increased risk of oral motor dysfunction if they treat both.

In conclusion, BoNT-A injections can reduce saliva production and constitute one of the treatment options for children with CNS disorders and excessive drooling. However, in one-third of the treatments, mild and transient oral motor problems can be expected. A diagnosis of CP, higher BoNT-A dosage, and mild visible drooling at baseline are associated with an increased risk of oral motor problems. However, more scientific research at both the neurophysiological level (i.e. determinants of the entire pharyngeal swallowing process) and the pharmaceutical level (dose and concentration-finding) is needed. Moreover, such treatment and subsequent follow-up should preferably take place under the responsibility of a multidisciplinary saliva control team that is capable of anticipation and immediate management of adverse effects.

ACKNOWLEDGEMENTS

Thanks to the children and their parents for their participation, and Mrs. S De Groot for assessing the children. The authors have stated that they had no interests which may be perceived as posing a conflict or bias.

REFERENCES

1. Reddihough D, Erasmus CE, Johnson H, et al. Botulinum toxin assessment, intervention and aftercare for paediatric and adult drooling: international consensus statement. *Eur J Neurol* 2010; **17**(Suppl 2): 109–21.
2. Parkes J, Hill N, Platt MJ, Donnelly C. Oromotor dysfunction and communication impairments in children with cerebral palsy: a register study. *Dev Med Child Neurol* 2010; **52**: 1113–19.
3. Reid SM, McCutcheon J, Reddihough DS, Johnson H. Prevalence and predictors of drooling in 7- to 14-year-old children with cerebral palsy: a population study. *Dev Med Child Neurol* 2012; **54**: 1032–36.

4. Van De Heyning PH, Marquet JF, Creten WL. Drooling in children with cerebral palsy. *Acta Otorhinolaryngol Belg* 1980; **34**: 691–705.
5. van der Burg JJ, Jongerius PH, van Limbeek J, van Hulst K, Rotteveel JJ. Social interaction and self-esteem of children with cerebral palsy after treatment for severe drooling. *Eur J Pediatr* 2006; **165**: 37–41.
6. Scheffer AR, Erasmus C, van Hulst K, et al. Efficacy and duration of botulinum toxin treatment for drooling in 131 children. *Arch Otolaryngol Head Neck Surg* 2010; **136**: 873–77.
7. Vaile L, Finlay F. Is injection of botulinum toxin type A effective in the treatment of drooling in children with cerebral palsy? *Arch Dis Child* 2006; **91**: 862–63.
8. Reid SM, Johnstone BR, Westbury C, Rawicki B, Reddihough DS. Randomized trial of botulinum toxin injections into the salivary glands to reduce drooling in children with neurological disorders. *Dev Med Child Neurol* 2008; **50**: 123–28.
9. Moller E, Pedersen SA, Vinicoff PG, et al. Onabotulinumtoxin A treatment of drooling in children with cerebral palsy: a prospective, longitudinal open-label study. *Toxins (Basel)* 2015; **7**: 2481–93.
10. Porte M, Chaleat-Valayer E, Patte K, et al. Relevance of intraglandular injections of Botulinum toxin for the treatment of sialorrhea in children with cerebral palsy: A review. *Eur J Paediatr Neurol* 2014; **18**: 649–57.
11. Suskind DL, Tilton A. Clinical study of botulinum-A toxin in the treatment of sialorrhea in children with cerebral palsy. *Laryngoscope* 2002; **112**: 73–81.
12. Pena AH, Cahill AM, Gonzalez L, et al. Botulinum toxin A injection of salivary glands in children with drooling and chronic aspiration. *J Vasc Interv Radiol* 2009; **20**: 368–73.
13. Gok G, Cox N, Bajwa J, et al. Ultrasound-guided injection of botulinum toxin A into the submandibular gland in children and young adults with sialorrhoea. *Br J Oral Maxillofac Surg* 2013; **51**: 231–33.
14. Khan WU, Campisi P, Nadarajah S, et al. Botulinum toxin A for treatment of sialorrhea in children: an effective, minimally invasive approach. *Arch Otolaryngol Head Neck Surg* 2011; **137**: 339–44.
15. van Hulst K, Lindeboom R, van der Burg J, Jongerius P. Accurate assessment of drooling severity with the 5-minute drooling quotient in children with developmental disabilities. *Dev Med Child Neurol* 2012; **54**: 1121–26.
16. Erasmus CE, Van Hulst K, Rotteveel LJ, et al. Drooling in cerebral palsy: hypersalivation or dysfunctional oral motor control? *Dev Med Child Neurol* 2009; **51**: 454–59.
17. Hockstein NG, Samadi DS, Gendron K, Handler SD. Sialorrhea: a management challenge. *Am Fam Physician* 2004; **69**: 2628–34.
18. Nordgarden H, Osterhus I, Moystad A, et al. Drooling: are botulinum toxin injections into the major salivary glands a good treatment option? *J Child Neurol* 2012; **27**: 458–64.
19. Chan KH, Liang C, Wilson P, Higgins D, Allen GC. Long-term safety and efficacy data on botulinum toxin type A: an injection for sialorrhea. *JAMA Otolaryngol Head Neck Surg* 2013; **139**: 134–38.
20. Reid SM, Walstab JE, Chong D, Westbury C, Reddihough DS. Secondary effects of botulinum toxin injections into salivary glands for the management of pediatric drooling. *J Craniofac Surg* 2013; **24**: 28–33.
21. Erasmus CE, Van Hulst K, Van Den Hoogen FJ, et al. Thickened saliva after effective management of drooling with botulinum toxin A. *Dev Med Child Neurol* 2010; **52**: e114–18.
22. van den Engel-Hoek L, de Groot IJ, Esser E, et al. Biomechanical events of swallowing are determined more by bolus consistency than by age or gender. *Physiol Behav* 2012; **106**: 285–90.
23. Kim Y, McCullough GH, Asp CW. Temporal measurements of pharyngeal swallowing in normal populations. *Dysphagia* 2005; **20**: 290–96.
24. Tighe D, Gok G, Moody A, Howlett D. Dysphagia as a complication of botulinum toxin injections to treat drooling. *Br J Oral Maxillofac Surg* 2014; **52**: 673–74.
25. Papavasiliou AS, Nikaina I, Foska K, et al. Safety of botulinum toxin A in children and adolescents with cerebral palsy in a pragmatic setting. *Toxins (Basel)* 2013; **5**: 524–36.
26. O'Flaherty SJ, Janakan V, Morrow AM, Scheinberg AM, Waugh MC. Adverse events and health status following botulinum toxin type A injections in children with cerebral palsy. *Dev Med Child Neurol* 2011; **53**: 125–30.

New from Mac Keith Press

International Review of Child Neurology Series

Neonatal Seizures

Current management and future challenges

Edited by **Lakshmi Nagarajan**

- Describes up-to-date diagnostic and management guidelines to improve outcomes.
- Outlines current treatment strategies and decisions at the point of care.
- Integrates basic science with clinical features.

Contact us at **admin@mackeith.co.uk** to receive full table of contents and further details.
March 2016 / Hardback / 214 pp / 240 x 172mm / ISBN 978-1-909962-67-5 / £44.99
mackeith.co.uk