Changes in severity and impact of drooling after submandibular gland botulinum neurotoxin A injections in children with neurodevelopmental disabilities

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ABBREVIATIONS

DQ5	5-minute Drooling Quotient
NRG	Non-responder group
VAS	Visual Analogue Scale

AIMS To examine changes in objective and subjective drooling severity measures after submandibular botulinum neurotoxin A injection in children with neurodevelopmental disabilities, explore their relationship, and evaluate if clinically relevant responses relate to changes in the impact of drooling.

METHOD This longitudinal, observational cohort study involved 160 children (92 males, 68 females; 3–17y, mean 9y 1mo, SD 3y 6mo) treated between 2000 and 2012 at the Radboud University Medical Center, Nijmegen, the Netherlands. Repeated measures analysis of variance was used to compare the 5-minute Drooling Quotient (DQ5) and Visual Analogue Scale (VAS) for drooling severity pretreatment and posttreatment, and Pearson's rho to assess their association. A parent questionnaire was used to assess drooling impact in responders (defined as ≥50% reduction in DQ5 and/or ≥2 SD reduction in VAS for drooling severity 8wks postintervention) and non-responders.

RESULTS One hundred and twelve children (70%) were responders. Their mean VAS for drooling severity and DQ5 scores were significantly lower 32 weeks postintervention compared to baseline. At baseline, the VAS for drooling severity-DQ5 relationship was 'weak' (r_s=0.15, p=0.060), whereas it was 'fair' at 8 weeks (r_s=0.43, p=0.000) and 32 weeks (r_s=0.30, p=0.000). For responders, a significant change was found regarding the impact of drooling on daily care and social interactions at 8 weeks after intervention; most of these effects were maintained at 32 weeks.

INTERPRETATION A clinically relevant response based on a combination of objective and subjective measures of drooling severity was accompanied by positive changes regarding the impact of drooling on daily care and social interactions.

Botulinum neurotoxin A (BoNT-A) injections into the salivary glands are an accepted treatment option to treat drooling in children with cerebral palsy (CP) and other neurodevelopmental disabilities. After initial case studies,[1,2] reduction of salivary flow and its effect on drooling frequency and severity have been documented in cohort and controlled studies including randomized controlled trials.[3–8] In a systematic review, Rodwell et al.[9] concluded that BoNT-A is a temporary effective treatment. Outcomes in these studies included both objective and subjective measures, such as flow rate, Drooling Quotient,[10,11] Visual Analogue Scale (VAS),[12] Drooling Severity and Frequency Scale,[13] and the Teacher Drool Scale.[14]

Only a few studies have evaluated changes in the impact of drooling on children and their families. In a randomized controlled trial, Reid et al.[5] evaluated the effect of BoNT-A injections into the submandibular and parotid glands in 61 children with developmental disabilities. They found a highly significant difference in mean scores on the Drooling Impact Scale between the treatment and control group at 1-month follow-up.[5,15] The most significant changes were found in items addressing the severity and frequency of drooling and the number of bibs and clothing changed daily. They defined non-response to BoNT-A treatment as a reduction of less than 10 points on the Drooling Impact Scale (100-point scale). In a controlled clinical trial (n=45)[4] comparing bilateral submandibular BoNT-A injections to scopolamine treatment, parents reported changes in the impact of drooling for up to 24 weeks.[16] Clinically notable responses were found in the frequency parents wiped their children's chins and changed their bibs, making daily care less demanding. After intervention, the number of parents

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reporting damage to electronic devices and computers decreased. In addition, children's social contacts with peers increased. Parents also indicated that the perceived impact of drooling on their child's satisfaction concerning physical appearance, relationships within the family, and life in general, improved. Since only a few parents in this study observed an overt emotional reaction by the child concerning the impact of drooling, no significant changes in self-esteem could be established during the follow-up period.

Studies on the effect of BoNT-A treatment for drooling in larger groups of children with neurodevelopmental disabilities have appeared in the literature.[7,17] However, changes in drooling and the possible impact of such changes on the daily lives of the children and their parents are generally not reported.[18]

The Saliva Control Clinic at the Radboud University Medical Center, Nijmegen, the Netherlands, has systematically collected objective and subjective outcome measures at baseline and after 8 and 32 weeks to evaluate the effectiveness of medical interventions for drooling.

Our aims were to: (1) examine changes in both objective (5-minute Drooling Quotient [DQ5]) and subjective (VAS for drooling severity) measures of drooling severity and explore the relationship between these measures up to 32 weeks after first bilateral submandibular BoNT-A injection in children with CP or other neurodevelopmental disabilities; and (2) evaluate if a clinically relevant response to treatment (in accordance with our definition of clinical response) was related to parental report of changes in the impact of drooling on daily life.

What this paper adds

- Botulinum neurotoxin A injection into the submandibular glands reduced drooling severity in 70% of children with neurodevelopmental disabilities.
- Objective (5-minute Drooling Quotient) and subjective (Visual Analogue Scale for drooling severity) measures correlated 8 and 32 weeks after treatment.
- Objective and subjective measures complemented each other when changes in drooling severity were assessed.
- Reduced drooling severity was accompanied by positive changes with regard to the impact of drooling.

METHOD

Inclusion

Figure S1 (online supporting information) shows study enrolment and participant inclusion in this observational study. During the 2000 to 2012 period, after standardized assessment of swallowing, children eligible to participate underwent first-time BoNT-A submandibular treatment (n=160). Informed consent for BoNT-A treatment was obtained from the child's legal representative(s). The study was conducted in accordance with national and international ethical standards and was approved by the medical ethical committee of the Radboud University Nijmegen Medical Centre (CMO: 2018-4954).

BoNT-A procedure

Bilateral injections into the submandibular glands with BoNT-A (Botox; Allergan) were performed by the same physician (PJ) using ultrasound guidance and general anaesthesia. Botox was diluted in 0.9% saline solution (25U/ml) and 1ml was administered over two or three sites throughout the gland using a Spinocan needle (25 Ga; B. Braun Medical B.V., Oss, the Netherlands).

Outcome measures

During outpatient visits before injection (baseline) and 8 and 32 weeks after intervention, drooling severity was assessed with the DQ5 and VAS. The DQ5 was measured by a team speech and language therapist and carried out under standardized conditions during an individualized seated activity.[11] During this 5-minute observation, the presence or absence of new saliva was determined at 15-second intervals. The DQ5 is expressed as the percentage of observed drooling episodes (intervals with new saliva) and total number of intervals (0=no new saliva, 100=100% of intervals with new saliva).

At each of the three time points, parents also completed a VAS regarding drooling severity (VAS for drooling severity; 0=no drooling, 100=excessive drooling) and a parent questionnaire (Appendix S1, online supporting information) on the impact of drooling.[12,19] This questionnaire evaluates the impact of drooling on daily life and care, social interactions, and self-esteem.[16] It was developed by our saliva control team[20] and shortened to enhance applicability.[19] Earlier studies showed that this questionnaire picks up changes in the impact of drooling after intervention.[12,16,19]

A clinical response was defined as a ≥50% reduction in the DQ5 and/or a reduction of equal to or more than 2 SDs of the VAS for drooling severity 8 weeks postintervention compared to baseline.[17]

Data analysis

To evaluate the effects of BoNT-A intervention on drooling severity over time, a repeated measures analysis of variance (ANOVA) was used to analyse the DQ5 and VAS for drooling severity scores. The baseline DQ5 and VAS for drooling severity scores were compared at 8 and 32 weeks; a further comparison was made between 8 and 32 weeks. The Greenhouse–Geisser correction was used whenever the assumption of sphericity was violated, according to Mauchly's sphericity test. Post hoc tests were performed to interpret significant changes using Bonferroni correction (i.e. p=0.05/number of tests). The Friedman test was used for nominal and ordinal variables (questions 6–10) to evaluate the effects over time. Changes in daily care (parent questionnaire, questions 3–5) were analysed using the repeated measures ANOVA (interval data) for the responder and non-responder group (NRG).

Pearson's rho was used to study the correlation between the outcomes of the objective (DQ5) and subjective (VAS for drooling severity) measures at baseline and 8 and 32 weeks after intervention. It was interpreted as suggested by Portney and Watkins (0.0–0.25 weak or no relationship;

0.25–0.5 fair relationship; 0.5–0.75 moderate-to-good relationship; >0.75 excellent relationship).[21]

To explore the different options when evaluating change after BoNT-A treatment, we have critically reflected on our response definition and presented the data of the parent questionnaire for the responder group and NRG.

To describe and analyse the data regarding the impact of drooling on self-esteem (questions 11–14; Appendix S1), the VAS scores (0=very dissatisfied, 100=very satisfied) concerning satisfaction with: (1) social contact; (2) physical appearance; (3) relations within the family; and (4) life in general, were recoded into three categories: 0–32 (dissatisfied); 33–66 (neutral); and 67–100 (satisfied), as described previously by Kok et al.[19] The VAS scores for the extent to which drooling contributes to the level of satisfaction (0=not at all, 100=very important) on these 4 elements were also recoded in three categories: 0–32 (low contribution); 33–66 (neutral); and 67–100 (high contribution). For each question in the section on self-esteem, we determined the number of participants that combined dissatisfaction (VAS 0–32) with a high contribution (VAS 67–100) of drooling.

A pooled multiple imputation method (five iterations) was used to deal with missing values at baseline. To avoid bias in favour of positive outcomes, missing values at 8 or 32 weeks were imputed using a worst-case scenario: a missing value during follow-up was replaced by its baseline value. If both baseline and follow-up values were missing, no imputation was performed and the participant was omitted from the analysis for that item. Statistical analyses were performed using SPSS 21.0 for Windows (IBM Corp., Armonk, NY, USA).

RESULTS

Participants

Of the 160 participants, 92 were males and 68 females (Table 1). Chronological age at the injection date varied from 3 to 17 years (mean 9y 1mo, SD 3y 6mo). All children had neurodevelopmental disabilities and 123 children (76.9%) were diagnosed with CP (Gross Motor Function Classification System[22] level: I [*n*=2]; II [*n*=18]; III [*n*=27]; IV [*n*=33]; V [*n*=43]). Of the children without CP, 31 could walk and six could not. Eighty-two children were diagnosed with epilepsy (of these, 18 had uncontrolled epilepsy). The developmental age of children was determined based on information provided by their schools, day centres, and/or parents. In 87 children (54.4%), developmental age was below 4 years, in 39 children (24%) developmental age was between 4 and 6 years, and in 28 children (17.5%) developmental age was above 6 years. Data from five children were missing (3.1%). Following standardized assessment of swallowing by specialized speech and language therapists, 109 children (68.1%) had oral dysphagia and 49 (30.6%) had oropharyngeal dysphagia. Twelve children (7.5%) were partially dependent on tube feeding, eight (5.0%) were fully tube-fed and had no oral intake, 138 (86.3%) had only oral feeding, and the feeding data for two children (1.3%) were missing. All baseline measures were taken before the BoNT-A injections (mean 2.88mo, SD 2.45mo). At baseline, the mean VAS for drooling severity score was 78.09 (SD 17.74) and the mean DQ5 score was 32.43 (SD 22.15).

Almost all demographic data in the responder group and NRG were comparable. We only found a significant difference in diagnosis (p=0.013). In the responder group (*n*=112), 80 (71.43%) children were diagnosed with CP, whereas 32 (28.57%) had a different non-progressive neurodevelopmental disability, for example, a syndrome or genetic disorder. The NRG (*n*=48) consisted of 43 children (89.58%) with CP and 5 children (10.42%) with different neurodevelopmental disabilities.

In total, there were 16.6% missing values on the parent questionnaire due to incomplete or incorrect answers. Consequently, there was a difference in the number of children analysed for the different items in the questionnaire. There were no missing values in the DQ5 and VAS for drooling severity measurements.

Table 1: Characteristics of participants at baseline (total and RG and NRG) and mean outcomes on DQ5 and VAS_{-DS}

Patient characteristics	*n* total (%)	*n* RG (%)	*n* NRG (%)
Sex			
Male	92 (57.5)	62 (55.4)	30 (62.5)
Female	68 (42.5)	50 (44.6)	18 (37.5)
Diagnosis			
CP	123 (76.9)	80 (71.4)	43 (89.6)
Non-CP[a]	37 (37.3)	32 (28.6)	5 (10.4)
Epilepsy			
Absent	77 (48.1)	58 (51.8)	19 (39.6)
Controlled	64 (40.0)	44 (39.3)	20 (41.7)
Uncontrolled	18 (11.3)	9 (8.0)	9 (18.8)
Unknown	1 (0.6)	1 (0.9)	0
Mental ability			
Developmental age <4y	87 (54.4)	61 (54.5)	26 (54.2)
Developmental age 4–6y	39 (24.0)	29 (25.9)	11 (22.9)
Developmental age >6y	28 (17.5)	19 (17.0)	9 (18.8)
Unknown	5 (3.1)	3 (2.7)	2 (4.2)
Degree of mobility[b]			
Ambulant	82 (51.3)	57 (49.1)	23 (48)
Non-ambulant	78 (48.7)	55 (50.9)	25 (52)
Dysphagia			
Oral dysphagia	109 (68.1)	81 (72.3)	28 (58.3)
Oropharyngeal dysphagia	49 (30.6)	29 (25.9)	20 (41.7)
Unknown	2 (1.3)	2 (1.8)	0
Nutrition intake			
Tube and oral	12 (7.5)	7 (6.3)	5 (10.4)
Tube	8 (5.0)	6 (5.4)	2 (4.2)
Oral	138 (86.3)	97 (86.6)	41 (85.4)
Unknown	2 (1.3)	2 (1.8)	0
Patient data	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Age at inclusion (Y/mo)	9.1 (3.6)	9.4 (3.6)	8.7 (3.4)
DQ5	32.43 (22.15)	33.89 (22.6)	29.42 (20.52)
VAS_{-DS}	78.09 (17.74)	79.10 (17.1)	75.75 (19.10)

RG, responder group; *n*, number; NRG, non-responder group; CP, cerebral palsy; Y, year; mo, months; DQ5, drooling quotient 5 minutes; VAS_{-SD}, visual analogue scale drooling severity; SD, Standard deviation. [a]Non CP= children with developmental disability mainly as part of a syndrome, genetic, metabolic or neurodegenerative disorder. [b]Mobility: Ambulant: Children with CP with GMFCS I,II and III, and ambulant non-CP children. Non-ambulant: Children with CP with GMFCS IV and V, and wheelchair depended non-CP children.

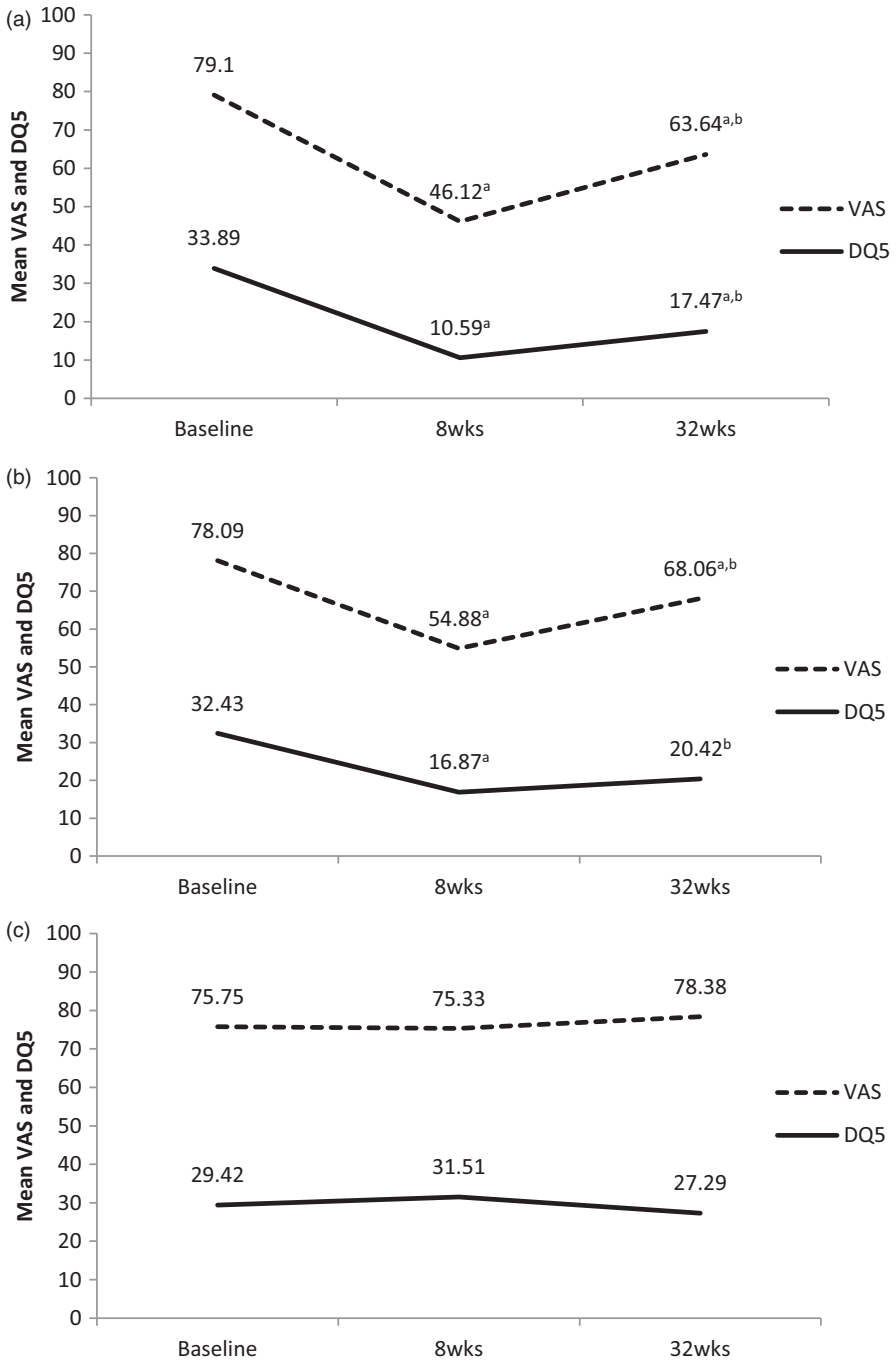

Figure 1: Mean drooling severity based on the Visual Analogue Scale (VAS) for drooling severity and 5-minute Drooling Quotient (DQ5) at baseline and 8 and 32 weeks after submandibular botulinum neurotoxin A injections for: (a) the whole cohort (*n*=160), (b) the responder group (*n*=112), and (c) the non-responder group (*n*=48). [a]Significant change between baseline and 8 weeks or between 8 weeks and 32 weeks. [b]Significant change between baseline and 32 weeks.

Clinical response

Eight weeks after BoNT-A injections, 94 children (58.8%) showed ≥50% reduction in DQ5, while 58 children (36.3%) showed a ≥2 SD reduction in VAS for drooling severity from baseline VAS (drooling severity). Forty children met both criteria. Applying our definition of clinical response, 112 children (70%) experienced a 50% reduction in DQ5 and/or a 2 SD reduction (2 SD=35.48) in VAS for drooling severity 8 weeks after injection. Thus, they were considered responders.

Drooling severity: relationship between objective and subjective measures

Figure 1a shows the reduction in drooling severity as the mean VAS for drooling severity and DQ5 scores for the entire cohort of participants (n=160) over time. The repeated measures ANOVA revealed that the mean VAS for drooling severity and DQ5 scores differed significantly between time points (VAS for drooling severity: F[1.927, 306.382]=48.96, p=0.000; DQ5: F[1.856, 295.136]=54.64, p=0.000). Post hoc tests revealed a significant decrease in both mean VAS for drooling severity (p=0.000) and DQ5 (p=0.000) scores between baseline and follow-up at 8 weeks. Between 8 and 32 weeks, there was a significant increase in drooling severity for the mean VAS for drooling severity (p=0.000) and DQ5 (p=0.027) scores, although both mean scores at 32 weeks indicated that drooling severity remained significantly below baseline level. The time effects between baseline and 32 weeks were still significant for both measurements (VAS for drooling severity [p=0.000]; DQ5 [p=0.000]).

Regarding correlation, there was a weak relationship between VAS for drooling severity and DQ5 at baseline (r_s=0.15, p=0.060). However, at 8 (r_s=0.43, p=0.000) and 32 weeks (r_s=0.30, p=0.000) the relationship was 'fair'.

Figure 1b,c outlines the changes in drooling severity for the responder group and NRG up to 32 weeks. As expected, the responder group showed significant differences between the three time points for both VAS for drooling severity (F[2.222]=66.54, p=0.000) and DQ5 (F [1.863, 206.743]=92.36, p=0.000). In the NRG, changes between all time points for both VAS for drooling severity (F[1.729, 81.242]=0.58, p=0.539) and DQ5 (F[2,94]=1.49, p=0.232) were not significant.

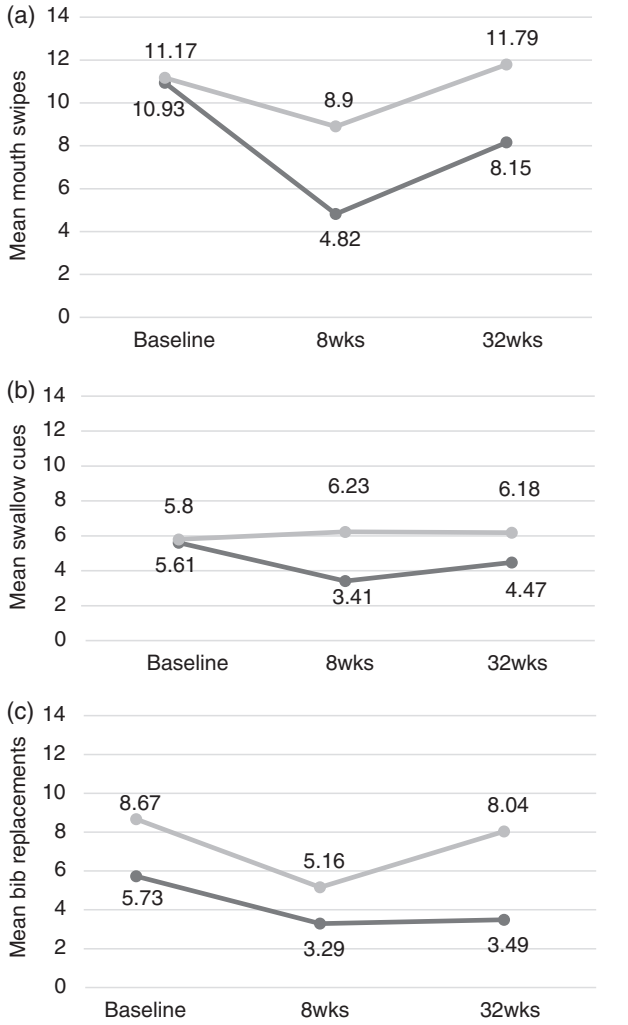

Figure 2: Change in the impact of drooling on daily care in non-responder (NRG) (light grey lines) and responder groups (dark grey lines). (a) Mean mouth wiping. NRG (n=42): no significant change before and after botulinum neurotoxin A (BoNT-A) injection (F[2,82]=2.332, p=0.104). Responder group (n=101): baseline to 8 weeks (mean=6.11, p=0.000, 95% confidence interval [CI]=3.33–8.89); baseline to 32 weeks (mean=2.78, p=0.000, 95% CI=1.36–4.20); 8–32 weeks (mean=−3.33, p=0.006, 95% CI=−5.88 to −0.77). (b) Mean swallowing cues. NRG (n=44): no significant change before and after BoNT-A injection (F[1.630, 70.086]=0.12, p=0.845). Responder group (n=108): baseline to 8 weeks (mean=2.20, p=0.002, 95% CI=0.69–3.72); baseline to 32 weeks (mean=1.14, p=0.054, 95% CI=−0.14 to 2.29); 8–32 weeks (mean=−1.06, p=0.152, 95% CI=−2.37 to 0.25). (c) Mean bib replacement. NRG (n=45): baseline to 8 weeks (mean=3.51, p=0.02, 95% CI=0.44–6.58), baseline to 32 weeks (mean=0.62, p=1.00, 95% CI=−1.38 to 2.63); 8–32 weeks (mean=−2.89, p=0.10, 95% CI=−6.17 to 0.39). Responder group (n=112): baseline to 8 weeks (mean=2.44, p=0.000, 95% CI=1.57–3.31); baseline to 32 weeks (mean=2.24, p=0.004, 95% CI=0.60–3.89); 8–32 weeks (mean=−0.20, p=1.00, 95% CI=−1.78 to 1.39).

Changes in the impact of drooling based on the parent questionnaire

Impact of drooling on daily care and economic consequences (part 2 of questionnaire)

Figure 2 shows the changes in daily care at the three time points (frequency of mouth wiping [Fig. 2a], verbal prompts to swallow [Fig. 2b], and bib replacement [Fig. 2c]) for the responder group and NRG respectively.

The repeated measures ANOVA indicated that the frequency of wiping the mouth and chin by the parents of responders (n=101) decreased significantly over time (F[1.417, 141.706]=20.43, p=0.000). Post hoc tests revealed a significant decrease in mouth wiping between baseline and 8 weeks, baseline and 32 weeks, and at the 8- and 32-week follow-up. In the NRG (n=42), no significant changes over time were found regarding the frequency of mouth wiping.

The frequency of verbally prompting a child to swallow in the responder group (n=108) decreased significantly from baseline to the 32-week follow-up (F[1.819, 194.609] =8.07, p=0.001). Post hoc tests revealed a significant decrease between baseline and 8 weeks after BoNT-A injection, but the scores almost returned to the baseline

level between 8 and 32 weeks. In the NRG (n=44), no significant changes over time were found in prompts to swallow.

From baseline to 32 weeks after BoNT-A injection, a significant decrease in the frequency of replacing the bibs was found in the responder group (F[1.443, 160.204] =10.86, p=0.000) and NRG (F[1.587, 69.822]=5.39, p=0.011). In the responder group (n=112), a significant decrease in replacing the bibs was found between baseline and 8 weeks and baseline and 32 weeks, whereas the change between 8 and 32 weeks was not significant. In the NRG (n=45), only the change between baseline and 8 weeks was significant.

Friedman's test indicated no significant changes in the number of parents in the responder group (n=112) who reported damage to computers or other devices during the study (χ^2[2]=5.786, p=0.055). However, in the NRG (n=48), changes were significant (χ^2[2]=9.692, p=0.008), suggesting that the number of parents reporting damage to computers or other devices decreased from 15 at baseline to 6 at 8 weeks, and then increased to 9 at 32 weeks. In the responder group, the number of parents who reported damage to floors and furniture decreased significantly (χ^2[2]=11.706, p=0.003; 35 at baseline, 20 at 8 weeks, and 22 at 32 weeks), whereas in the NRG these change were not significant (χ^2[2]=3.647, p=0.161).

Impact of drooling on social interaction (part 3 of questionnaire)

Table 2a illustrates the changes in social consequences for both responder group and NRG as reported by parents. In the responder group, there was a significant decrease in the number of parents who reported that: (1) their child was avoided by peers because of drooling (χ^2[2]=25.409, p=0.000), (2) their child was avoided by adults because of drooling (χ^2[2]=7.548, p=0.023), and (3) the cognitive ability of their child was underestimated because of drooling (χ^2[2]=12.742, p<0.001). In the NRG, decreases were not significant for all three items: (1) χ^2(2)=1.733, p=0.420; (2) χ^2(2)=0.667, p=0.717; and (3) χ^2(2)=4.429, p=0.109.

Impact of drooling on emotional development (self-esteem) (part 4 of questionnaire)

Parent impression. Across the study, only a few parents in both groups reported that their child felt dissatisfied during the previous 4 weeks regarding social contacts with other children, their physical appearance, relationships within the family, or their life in general because of

Table 2: Social consequences of drooling (part 3), impact on self-esteem (parent impression and emotional reactions of the child, [part 4]) at baseline (Bsl), and at 8 and 32 weeks after BoNT-A in the RG and NRG

	Responder group (n, %)			Non-responder group (n, %)		
	Bsl	8wks	32wks	Bsl	8wks	32wks
(a) Social consequences						
Avoided by other children because of drooling (nRG=112, nNRG=48)	56 (50)	30 (27.3)	34 (30.4)	21 (43.8)	18 (37.5)	22 (45.8)
Avoided by adults because of drooling (nRG=112, nNRG=48)	38 (33.9)	26 (23.2)	29 (25.9)	15 (31.3)	13 (27.1)	14 (29.2)
Underestimation of mental capacity because of drooling (nRG =110/109/109, nNRG =48)	36 (32.7)	22 (20.2)	24 (22)	10 (20.8)	15 (31.3)	16 (33.3)
(b) Impact on self-esteem; parent impression[a]						
Dissatisfied about social contact with other children because of drooling (nRG=102, nNRG=46)	3 (2.7)	1 (0.9)	2 (1.8)	3 (6.3)	3 (6.3)	1 (2.1)
Dissatisfied about physical appearance because of drooling (nRG=91/90/89, nNRG=41)	2 (1.8)	1 (0.9)	4 (3.6)	2 (4.2)	3 (6.3)	2 (4.2)
Dissatisfied about relationship within family because of drooling (nRG=104, nNRG=45)	3 (2.7)	0 (0)	1 (0.9)	2 (4.2)	1 (2.1)	0 (0)
Dissatisfied about life in general because of drooling (nRG=103, nNRG=46)	3 (2.7)	0 (0)	3 (2.7)	1 (2.1)	2 (4.2)	0 (0)
(c) Impact on self-esteem: emotional reactions of child						
Negative about physical appearance because of drooling (nRG=106, nNRG=45)	11 (10.4)	5 (4.7)	7 (6.6)	4 (8.9)	3 (6.7)	1 (2.2)
Negative about social acceptance by adults because of drooling (nRG=103, nNRG=44)	5 (4.9)	1 (1)	1 (1)	1 (2.3)	0 (0)	3 (6.8)
Negative about peer acceptance because of drooling (nRG=103, nNRG=44)	10 (9.7)	2 (1.9)	5 (4.9)	9 (20.5)	3 (6.8)	5 (11.4)

nRG, number of children in Responder Group; nNRG, number of children in Non-Responder Group. [a]Questions 11–14 questionnaire: number and percentage of parents reporting: (1) that their child was dissatisfied (Visual Analogue Scale [VAS]-score 0-32) and (2) that this was related to drooling (VAS 67-100 very important).

drooling. Table 2b shows the numbers and percentages for each item. Because of the small number of children for whom this was reported, no statistical analysis could be performed. Visual analysis showed a decline in all items in the responder group.

Emotional reactions of the child. Only a small number of children could articulate (verbally or with augmentative communication) positive or negative feelings about their appearance and social acceptance by adults or peers (Table 2c). At 8 weeks, the number of parents in this subgroup who reported negative feelings related to drooling as expressed by their child, decreased in both the responder group and NRG. At 32 weeks, the number of parents who reported the emotional reactions of their child increased, compared to that recorded at 8 weeks. No statistical analysis could be performed because of the small sample size.

DISCUSSION

This study of 160 children with neurodevelopmental disabilities strengthens the findings of previous studies that submandibular BoNT-A injections reduce the severity of drooling. We found a clinical response in 70% of children at 8 weeks postinjection based on our clinical definition. Remarkably, we found only a 'fair' correlation between objective and subjective outcome measures at 8 weeks posttreatment. Almost 60% of children showed a reduction ≥50% in the DQ5. A reduction ≥2 SD in the parental VAS for drooling severity was found in 36% of the children 8 weeks after BoNT-A injection. Apparently, the subjective opinion of parents with regard to the reduction of drooling severity in daily life did not match with the objective assessment of drooling. This discrepancy between objective and subjective assessments is a striking result of the present study and suggests that these two assessments do not reflect the same response dimension. Therefore, the DQ5 cannot simply be replaced by the VAS for drooling severity. This conclusion is in contrast with the one reached by Rashnoo et al.,[23] who found a strong correlation between the objective Drooling Quotient and the Drooling Severity and Frequency Scale, a subjective tool. They suggested that the Drooling Severity and Frequency Scale and Drooling Quotient are interchangeable when guiding the clinical management of drooling. However, the results of the current study indicate that a response definition based on a combination of objective and subjective measures is preferable.

The second aim of this study was to evaluate if a clinically relevant response to BoNT-A treatment was related to the parents' perspectives of meaningful change in the impact of drooling on daily care, economic consequences, and social and emotional aspects.[12,16] The results suggest that BoNT-A injections can make daily care for parents less demanding, as demonstrated by a significant decrease in mouth and chin wiping, fewer prompts to swallow being required, and fewer bib replacements needed. Observed group differences regarding changes in the impact of drooling on daily life between responder group and NRG seem to support our clinical response definition. Indeed, the decrease in the reported frequencies of mouth wiping and prompts to swallow was significant for the responder group, but not for the NRG. Although the mean amount of bib use was not equally divided between groups at baseline, mean bib replacement was significantly lower at 32 weeks in the responder group; in the NRG, it was lower only at 8 weeks after BoNT-A injection. However, the frequency of bib changing may not be a sensitive marker of treatment effect. Rashnoo et al.[23] found a rather weak association between the Drooling Quotient and the number of bib replacements. They argued that bib replacement is not a sensitive measure of clinical change after drooling treatment because parents may change the bib out of habit (e.g. after every meal) rather than to clear dampness. In our opinion, parent behaviour regarding bib change is more closely related to the severity of drooling as reflected in their VAS but not the DQ5 score.

As expected, the results for the social consequences of drooling showed differences between the responder group and NRG: only the parents of the responder group reported that children were less likely to be avoided by other children or adults and to be underestimated with regard to their cognitive capacity. For the emotional consequences of drooling, no substantial changes after BoNT-A injection could be established in either group, so only tentative conclusions may be drawn. This may be due to the small number of children who could reflect on this important subject: only 28 participants had an estimated developmental age above 6 years.

Not all results were in line with our definition of a good clinical response. For example, in the responder group no significant change was found in the number of parents who reported damage to computers or other devices before and after treatment. Surprisingly, a significant decrease in this item was found in the NRG after treatment. No clear explanation could be given for this finding and further research is necessary.

A strength of this observational study is the systematic way data were collected in a sample of 160 children. To our knowledge, this study represents the largest cohort of children where submandibular BoNT-A injection for drooling has been evaluated. All children were systematically selected from a tertiary outpatient clinic and received a first-ever bilateral submandibular BoNT-A injection for drooling. Treatment effect was monitored objectively and parents were asked to fill in questionnaires at baseline and again at 8 and 32 weeks after intervention.

Our study has several limitations. First, speech and language therapists were not blinded during the DQ5 observations. Second, the parent questionnaire has not yet been tested on all aspects of reliability and validity, but has been shown to be sensitive to change in previous research and in the current study.[12,16,19] A favourable aspect of the questionnaire is that analysis can be done per item, which gives a balanced opinion about (changes in) the impact of drooling on various aspects of daily life. Third, no guarantee

could be obtained whether the same parent completed the baseline and follow-up questionnaires, which might have affected response consistency over time. Another limitation is the low developmental age of the children involved. In our group of participants, 56% of children had a developmental age below 4 years. It may have been difficult for parents to report on the social and emotional consequences of drooling for these children. Lastly, with regard to the definition of clinically meaningful change, we acknowledge the limitation of using a dichotomous model of responders versus non-responders.

An important discussion relates to the perspective on improvement after an intervention for drooling; how to define a meaningful change? Change is a complex concept because it involves clinical and statistical considerations.[24] Change is closely related to the concept of difference, which is based on difference scores of measurable entities and is related to a time span in most instances. It can be argued that change should primarily be measured at a subjective individual level while ensuring that the measurement is objective and accurate. In our definition of clinical response, we combined objective (DQ5) and parent-reported subjective (VAS) outcomes for drooling severity. By relating this to parent-reported changes on the impact of drooling after BoNT-A injections, we tried to substantiate this definition as reflecting meaningful change. If we had only used the change in DQ5, there was a risk that relevant postintervention changes in the home setting would not have been included in the evaluation of effect. If we had only used the VAS as the outcome measure, the basic rule of science that conclusions must be based on objective measurements would have been ignored. Therefore, we recommend using the DQ5, VAS for drooling severity, and a questionnaire based on parental experience when assessing all aspects of drooling. Parents' experience of change in drooling severity and its impact after intervention are crucial to ensure their willingness to undertake further treatment. This is an important issue because BoNT-A injection is a temporary, albeit effective, treatment that requires general anaesthesia.

The population of children with chronic drooling is very heterogeneous with regard to cognitive and motor capacities. In the Netherlands, their social participation ranges from regular and special education to attendance at daycare centres and homes for young people with developmental disabilities. Consequently, the impact of drooling may be different for each individual and their relatives. Changes in the impact of drooling may be valued differently depending on the social and cultural situation within this heterogeneous population. From this perspective, we suggest a more personalized approach to the evaluation of drooling, where the meaningfulness of treatment results is considered in the context of the characteristics, circumstances, and opinions of the affected individual.

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SUPPORTING INFORMATION

The following additional material may be found online:

Figure S1: Flowchart of enrolment of participants with cerebral palsy or other neurodevelopmental disabilities.

Appendix S1: Drooling questionnaire.

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RESUMEN

Cambios en la severidad e impacto del babeo tras inyecciones de neurotoxina botulínica A en la glándula submandibular en niños con desórdenes del neurodesarrollo

OBJETIVO

Examinar los cambios en las medidas objetivas y subjetivas de la severidad del babeo después de la inyección submandibular de la neurotoxina A en niños con alteraciones en el neurodesarrollo, explorar su relación y evaluar si las respuestas clínicamente relevantes se relacionan con cambios en el impacto del babeo.

METODO

Este estudio de cohorte longitudinal y observacional incluyó 160 niños (92 niños, 68 niñas; de entre 3 y 17 años, de media de 9 años y 1 mes, DE 3 años y 6 meses) tratados entre el 2000 y el 2012 en el centro médico universitario Radboud de Nijmegen en los Países Bajos. Se utilizó un análisis de varianza de medidas repetidas para comparar el cociente de babeo de 5 minutos (siglas en inglés, 5-minute Drooling Quotient (DQ5) y la severidad del babeo pretérmino y postérmino con la escala visual analógica (EVA); así como el rho de Pearson para evaluar su asociación. Se utilizó un cuestionario de padres para evaluar el impacto del babeo en los niños que respondieron (definido como ≥50% de reducción en *DQ5* y / o ≥2 SD de reducción en EVA para la gravedad de babeo 8 semanas después de la intervención) y en los que no respondieron.

RESULTADOS

Ciento doce niños (70%) respondieron a la intervención. Su media EVA de severidad del babeo y la puntuación del *DQ5* fueron significativamente más bajos 32 semanas después de la intervención en comparación con el punto de partida. Al inicio, la relación entre la EVA de severidad del babeo y el *DQ5* fue débil (r_s=0.15, p=0.060), mientras que fue razonable a las 8 semanas (r_s=0.43, p=0.000) y a las 32 semanas (r_s=0.30, p=0.000). En los que respondieron a la intervención, se encontró un cambio significativo con respecto al impacto del babeo en el cuidado diario y las interacciones sociales a las 8 semanas después de la intervención; la mayoría de estos efectos se mantuvieron a las 32 semanas.

INTERPRETACION

La respuesta clínicamente relevante basada en la combinación de medidas objetivas y subjetivas de severidad del babeo se acompañó de cambios positivos en relación con el impacto del babeo en el cuidado diario y las interacciones sociales.

RESUMO

Mudanças na severidade e impacto da salivação após injeções de neurotoxina botulínica A na glândula submandibular em crianças com transtornos neurodesenvolvimentais

OBJETIVO

Examinar mudanças em medidas objetivas e subjetivas da severidade da salivação após injeção de neurotoxina botulínica A submandibular em crianças com transtornos neurodesenvolvimentais, explorar sua relação, e avaliar se respostas clinicamente relevantes se relacionam com mudanças no impacto da salivação.

MÉTODO

Este estudo longitudinal observacional de coorte envolveu 160 crianças (92 do sexo masculino, 68 do sexo feminino; 3–17a, média 9a 1m, DP 3a 6m) tratadas entre 2000 e 2012 no Centro Médico da Universidade Radboud, em Nijmegen, Holanda. Análise de variância de medidas repetidas foi usada para comparar o Quociente de Salivação em 5 minutos (QS5) e Escala Visual Analógica (EVA) para severidade da salivação pré e pós-tratamento; e rho de Pearson foi usado para avaliar sua associação. Um questionário parental foi usado para avaliar o impacto da salivação nos responsivos (definidos como redução ≥50% no QS5 e/ou redução ≥2 DP na EVA para severidade da salivação) 8 semanas pós-intervenção e não reponsivos.

RESULTADOS

Cento e doze crianças (70%) foram responsivas. A EVA média para severidade da salivação e os escores QS5 foram significativamente mais baixos 32 semanas pós-intervenção em comparação com a linha de base. Na linha de base, a relação VA para severidade da salivação com QS5 foi 'fraca (r_s=0,15, p=0,060), e 'moderada' em 8 (r_s=0,43, p=0,000) e 32 semanas (r_s=0,30, p=0,000). Para os respondentes, uma mudança significativa foi encontrada quanto ao impacto da salivação no cuidado diário e interações sociais 8 semanas após a intervenção; a maior parte destes efeitos foi mantida em 32 semanas.

INTERPRETAÇÃO

Uma mudança clinicamente relevante com base em uma combinação de medidas objetivas e subjetivas da severidade da salivação foi acompanhada de mudanças positivas no impacto da salivação no cuidado diário e interações sociais.