

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.

<https://repository.ubn.ru.nl/handle/2066/233385>

Please be advised that this information was generated on 2021-10-26 and may be subject to change.

Surgery versus botulinum neurotoxin A to reduce drooling and improve daily life for children with neurodevelopmental disabilities: a randomized controlled trial

STIJN BEKKERS^{1,*}  | INEKE M J PRUIJN^{1,*}  | JAN J W VAN DERBURG^{2,3} | KAREN VANHULST⁴  | SASKIA E KOK¹  | CORINNE P DELSING¹  | ARTHUR R T SCHEFFER¹ | FRANK J A VANDEN HOOGEN¹

1 Department of Otorhinolaryngology and Head and Neck Surgery, Radboud University Medical Center, Nijmegen; **2** Department of Pediatric Rehabilitation, Sint Maartenskliniek, Nijmegen; **3** School of Pedagogical and Educational Science, Radboud University, Nijmegen; **4** Department of Rehabilitation, Radboud University Medical Center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, the Netherlands.

Correspondence to Stijn Bekkers at Radboud University Medical Center, Philips van Leijdenlaan 15, Postbus 9101, 6500 HB, Nijmegen, the Netherlands. E-mail: stijn.bekkers@radboudumc.nl

*Shared first authorship.

PUBLICATION DATA

Accepted for publication 15th April 2021.

Published online

ABBREVIATIONS

DIS Drooling Impact Scale
RCT Randomized controlled trial

AIM To compare the effect of bilateral submandibular duct ligation and botulinum neurotoxin A (BoNT-A) on drooling severity and its impact on daily life and care in children and adolescents with moderate-to-severe drooling.

METHOD This was a randomized, interventional, controlled trial in which 53 children and adolescents (31 males, 22 females, mean age 11y, range 8–22y, SD 2y 10mo) with cerebral palsy (58.5%) or other non-progressive developmental disorders (41.5%) were randomized to BoNT-A ($n=26$) or bilateral submandibular duct ligation ($n=27$). A parent questionnaire on the severity of drooling in specific positions and daily activities and the impact of drooling on daily life and care was filled out at baseline and 8 and 32 weeks posttreatment.

RESULTS Both BoNT-A and bilateral submandibular duct ligation had a positive effect on daily care, damage to electronic equipment and/or furniture, social interactions, and self-esteem. However, bilateral submandibular duct ligation had a significant greater and longer-lasting short- (8wks) and medium-term (32wks) effect on daily care, reducing damage to electronic devices, and improving social interactions and satisfaction with life in general.

INTERPRETATION This randomized controlled trial confirms reduced drooling by both BoNT-A and bilateral submandibular duct ligation, but provides new evidence on improved well-being through a reduction in drooling. Even though there is a greater risk of complications and morbidity after bilateral submandibular duct ligation, compared to BoNT-A there was a significantly greater and longer-lasting positive effect on most outcomes.

Drooling (sialorrhoea), a prevalent problem (44%) in children with non-progressive neurodevelopmental disabilities, including cerebral palsy (CP),¹ has a substantial impact on the well-being and daily life of children and their caregivers. Frequent wiping and changing of bibs and clothes is required, while saliva damages perioral skin, clothes, communication aids, furniture, and floors. Beyond the physical implications, drooling may be a main source of social and emotional distress and may have a negative impact on self-esteem and participation in society, school activities, and family life.^{2–4} Additionally, drooling may lead to avoidance by others, social isolation, and an underestimation of mental capacities even though cognitive functions are not necessarily impaired.² Caregivers have expressed concern about the risk of embarrassment, social isolation, and stigmatization.³

When conservative treatment (oral motor or behavioural therapy) are ineffective, anticholinergics, botulinum

neurotoxin A (BoNT-A), or surgery may be considered. In our view, anticholinergics are currently only considered in case of lack of effect or contraindications to surgery or BoNT-A. While there is still a chance for patients to ‘out-grow’ drooling, BoNT-A could be considered from the age of 4 years onwards.⁵ Our saliva control team primarily focuses on the submandibular glands for interventional therapy since the submandibular glands are responsible for 70% of the total saliva production in the unstimulated state. Combined injections (parotid and submandibular) are only considered when there is no or inadequate response to submandibular BoNT-A to prevent patients from being overtreated when initially combining injections and to limit related morbidity.^{6,7}

Bilateral submandibular duct ligation was recently described as a short and simple day treatment procedure offering an alternative to BoNT-A and more invasive surgery, such as submandibular duct relocation and

submandibular gland extirpation.^{6,8} A recent randomized controlled trial (RCT) from our research group showed almost 90% treatment success in drooling reduction 8 weeks after bilateral submandibular duct ligation compared to a treatment success of 54% 8 weeks after submandibular BoNT-A, which is only slightly lower than treatment success after submandibular duct relocation and submandibular gland extirpation.^{9–13} In that trial, treatment success was defined as a 50% or more reduction in drooling quotient and/or caregiver score on a visual analogue scale. There was a slightly greater risk for complications and morbidity after bilateral submandibular duct ligation compared to BoNT-A.⁶ The cost-effectiveness analysis revealed that BoNT-A is less expensive per percentage of success than bilateral submandibular duct ligation. However, the additional cost of bilateral submandibular duct ligation over BoNT-A is offset by greater treatment success. The cost of both procedures is equal after approximately 1.5 BoNT-A injections.¹⁴ As part of this RCT, additional information was collected on the impact of drooling on well-being and daily care. The aim of this article is to report the effect of BoNT-A and bilateral submandibular duct ligation on drooling severity and its impact on daily life and care, damage to electronic devices and/or furniture, social interactions, and self-esteem in children with neurodevelopmental disabilities and moderate-to-severe drooling.

METHOD

Study design

This RCT was conducted at Radboud University Medical Center Nijmegen, the Netherlands between April 2012 and August 2017. Patients were randomly allocated to treatment with BoNT-A or bilateral submandibular duct ligation. There was partial blinding for treatment allocation. Investigators measuring the objective outcomes were masked, whereas patients and caregivers were not blinded to treatment allocation. For a detailed description of the study design, see Bekkers et al.⁶

Participants

Patients were recruited at the regular outpatient Saliva Control clinic of Radboud University Medical Center where these children and adolescents were assessed. The multidisciplinary team included a paediatric neurologist, a paediatric speech and language therapist, a rehabilitation specialist, a psychologist, and an ear, nose, and throat surgeon on consultation. All eligible patients underwent oral motor therapy to optimize swallowing and mouth closure skills before inclusion. All children and adolescents whose conservative treatment (speech and language or behavioural therapy) had failed or was not expected to provide substantial relief were considered for the study. Children were aged 8 years or older (when there is a low chance that children would still ‘outgrow’ drooling), diagnosed with CP or any other non-progressive neurodevelopmental disorder, and reported with moderate or severe drooling (defined as

What this paper adds

- Bilateral botulinum neurotoxin A (BoNT-A) and submandibular duct ligation had a positive effect on the well-being of individuals with moderate-to-severe drooling.
- Bilateral submandibular duct ligation had a greater effect on the impact of drooling during daily care than BoNT-A.
- Bilateral submandibular duct ligation reduced damage to electronic devices and improved social interactions and satisfaction with life.

a drooling frequency score ≥ 3 or drooling severity score ≥ 2).¹⁵

Interventions

Both BoNT-A injections and bilateral submandibular duct ligation were performed in an outpatient setting. BoNT-A (Allergan, Nieuwegein, the Netherlands) was administered to the submandibular glands under general anaesthesia, fractioning 25U in 0.9% saline over each submandibular gland using a 25-gauge needle and ultrasound guidance. Patients were treated under general anaesthesia and ultrasound guidance to decrease the risk of adverse events in the case of extra-glandular BoNT-A. In participants with previous BoNT-A treatment, BoNT-A injections or bilateral submandibular duct ligation were performed at least 6 months after the last injection to prevent a carry-over effect.

Bilateral submandibular duct ligation was also performed under general anaesthesia. The submandibular ducts were traced, dissected, and ligated, applying two metal vascular clips to each duct. Intraoral absorbable sutures closed the incision.⁶ All patients who had received bilateral submandibular duct ligation received amoxicillin/clavulanic acid and paracetamol plus diclofenac for 7 and 5 days respectively.

Outcome measures

A questionnaire was filled out by one of the parents or caregivers (hereafter referred to as caregivers) at the baseline measurement and 8 and 32 weeks posttreatment (Appendix S1, online supporting information). Drooling severity in 13 specific positions and daily activities (e.g. sitting, eating, relaxing; Appendix S1) and the impact of drooling on daily care, the child’s social interactions, and self-esteem were scored by the caregivers in the questionnaire. Caregivers were also asked the average number of times during the past 2 weeks they had to wipe the child’s chin (per hour), encourage the child to swallow (per hour), and change bibs (per day). Moreover, the questionnaire included a question of whether damage to furniture and/or electronic devices (communication aids, tablets, electronic wheelchair) had occurred due to drooling during the past 2 weeks (dichotomous yes or no answer). The questionnaire was originally developed by our multidisciplinary saliva control team to evaluate the effect of BoNT-A on the impact of drooling and has been shown to be sensitive to change over time.^{2,16–18} It contains multiple visual analogue scales, several multiple choice questions, and some open-ended questions.¹⁶

Statistical analysis

All data were analysed using SPSS 22.0 for Windows (IBM Corp., Armonk, NY, USA). Patients who crossed over to the other treatment arm were analysed according to the intention-to-treat principle. Patients who were excluded or withdrew from the study were not included in the analyses. Descriptive statistics were used to summarize patient characteristics. Paired and unpaired sample *t*-tests were used to compare normally distributed continuous variables, such as bib or shawl replacements, while ordinal level variables, including drooling severity, were compared using Mann–Whitney *U* and Wilcoxon tests and nominal level variables via χ^2 tests. Missing data were missing at random and automatically imputed 20 times by SPSS; they were stratified by treatment group, with all patient characteristics and clinical outcomes as variables in the model. Multiple imputation for missing data on the last three questions regarding emotional reactions (questions 15–17) were performed separately, excluding children with an estimated developmental age of less than 4 years since they were considered unable to express their feelings on physical appearance and social acceptance.^{16,17} Drooling severity in 13 positions and daily activities was analysed in children able to participate in the displayed positions and daily activities, excluding children to whom the position or daily activity was not applicable. Differences in change between interventions from baseline to 8 and 32 weeks were evaluated using mixed-model analysis for the continuous variables. Binary logistic regression was used to test for differences between treatments within dichotomous variables, with the intervention and baseline values as independent variables. A *p*-value of ≤ 0.05 was considered statistically significant and 95% confidence intervals (CIs) were given for the interpretation of the point estimates and significance levels.

Standard protocols, registrations, and patient consent

Approval of an independent regional ethics committee (Commissie Mensgebonden Onderzoek regio Arnhem – Nijmegen) and registration in the Dutch Trial Register (Netherlands Trial Register identifier: NTR3537) was obtained. Written and informed consent by caregivers or patients was provided for all participants.

Role of study sponsors

The study sponsors had no influence on the study design, collection of data, data analysis, interpretation of data, writing of the report, or decision to submit the paper for publication.

RESULTS

Of the 119 participants who were screened for eligibility, 40 did not meet the inclusion criteria and 22 declined participation, leaving 57 children and adolescents randomized to treatment allocation (Fig. S1, online supporting information). Fifty-three participants (31 males, 22 females, mean age 11y, range 8–22y, SD 2y 10mo) were analysed.

Three children did not receive the allocated intervention and one child crossed over to the BoNT-A arm because their caregivers preferred BoNT-A to bilateral submandibular duct ligation. Thirty-one children were diagnosed with CP, while 22 children had other unexplained neurodevelopmental disabilities mainly based on a syndrome (Pitt–Hopkins, cri du chat, distal 18q, Sjögren–Larsson, Marden–Walker, ATR–X), genetic (deletions or trisomy), or metabolic (mitochondrial) disorder. Baseline assessments were obtained at an average of 18 weeks (SD 15wks) before intervention. Four children were previously treated with anticholinergics, which were stopped due to adverse events or lack of effect. Patient characteristics and the number of preceding submandibular BoNT-A injections did not differ significantly between the BoNT-A and bilateral submandibular duct ligation group (Table 1).⁶

Drooling severity

Caregivers marked the severity of drooling in 13 positions and daily activities as not applicable (99), none (1), mild (2), moderate (3), severe (4), or very severe (5). For some participants, positions and daily activities were not applicable in supported sitting (BoNT-A=1; bilateral submandibular duct ligation=1), unsupported sitting (BoNT-A=1; bilateral submandibular duct ligation=3), prone position (BoNT-A=5; bilateral submandibular duct ligation=5), walking (BoNT-A=9; bilateral submandibular duct ligation=12), intensive movements (BoNT-A=7; bilateral submandibular duct ligation=7), tired (BoNT-A=0; bilateral submandibular duct ligation=0), eating (BoNT-A=4; bilateral submandibular duct ligation=3), drinking (BoNT-A=4; bilateral submandibular duct ligation=5), talking (BoNT-A=9; bilateral submandibular duct ligation=8), concentrated activity (BoNT-A=3; bilateral submandibular duct ligation=2), relaxed, watching TV (BoNT-A=2; bilateral submandibular duct ligation=1), strenuous activity (BoNT-A=1; bilateral submandibular duct ligation=1), and enthusiastic (BoNT-A=0; bilateral submandibular duct ligation=0) respectively. Excessive drooling (i.e. severe or very severe drooling) at baseline was most common in a prone position (89%) or during intensive movement (sport) (83%) and least reported during talking (49%) or drinking (53%). Eight weeks after BoNT-A and bilateral submandibular duct ligation, caregivers reported reduced drooling in all positions and daily activities (Fig. 1). Thirty-two weeks after treatment, the degree of drooling remained decreased in all positions and daily activities for the bilateral submandibular duct ligation group ($p < 0.001$) except for walking, in contrast to children who underwent BoNT-A, whose drooling severity had not significantly decreased during walking, intensive movements, or eating and even significantly increased during drinking, talking, and strenuous activity compared to baseline as illustrated by Figure 1. The mean percentage of excessive drooling from all 13 positions and daily activities together dropped from 74% to 46% 8 weeks after BoNT-A (mean difference=28.2, $p < 0.001$, 95% CI 19.4–37.1) but increased again to 66%

Table 1: Baseline demographic and clinical characteristics of the intention-to-treat population

	BoNT-A (n=26)	Bilateral submandibular duct ligation (n=27)	p
Age, y:mo, mean (SD)	11:2 (2:6)	11:1 (3:2)	0.93
Female sex	11 (42.3)	11 (40.7)	0.91
Main diagnosis			
Spastic CP	10 (38.5)	6 (22.2)	0.46
Dyskinetic CP	1 (3.8)	3 (11.1)	
Spastic/dyskinetic CP	5 (19.2)	5 (18.5)	
CP type missing	1 (3.8)	0	
Other non-progressive neurodevelopmental disorder ^a	9 (34.6)	13 (48.1)	
GMFCS level ^b (n=31)	n=17	n=14	0.33
II	2 (11.8)	1 (7.1)	
III	3 (17.6)	0	
IV	5 (29.4)	8 (57.1)	
V	7 (41.2)	5 (35.7)	
Mobility			
Ambulant	11 (42.3)	10 (37)	0.70
Non-ambulant	15 (57.7)	17 (63)	
Estimated developmental age			
<4y	15 (57.7)	15 (55.6)	0.88
≥4y	11 (42.3)	12 (44.4)	
Epilepsy			
Yes	17 (65.4)	15 (55.6)	0.47
Controlled	13 (76.5)	13 (86.7)	0.66
Intractable	4 (23.5)	2 (13.3)	
No	9 (34.6)	12 (44.4)	
Gastrostomy feeding			
Oral	16 (61.5)	20 (74.1)	0.33
Gastrostomy/gastrostomy and oral (no pharyngeal swallowing problem)	10 (38.5)	7 (25.9)	
Underwent BoNT-A pre-trial			
No	11 (42.3)	10 (37)	0.70
Yes	15 (57.7)	17 (63)	
Number of received submandibular BoNT-A injections, mean (SD)	1.6 (1.8)	1.4 (1.3)	0.19
Time since last BoNT-A injection, y:mo, mean (SD)	1:1 (0:8)	2:0 (2:10)	0.26

Data are n (%) unless otherwise stated. BoNT-A, botulinum neurotoxin A; CP, cerebral palsy; GMFCS, Gross Motor Function Classification System. ^aDisorders mainly based on a syndrome (Pitt-Hopkins, cri-du-chat, distal 18q, Sjögren-Larsson, Marden-Walker, ATR-X), genetic (deletions or trisomy), or metabolic (mitochondrial) disorder. ^bOnly applicable in children with CP (n=31). GMFCS levels I to III, ambulant; GMFCS IV and V, non-ambulant. *p*<0.05 was considered statistically significant.

32 weeks after BoNT-A (mean difference from baseline=7.6, *p*=0.009, 95% CI 2.3–13.0). For bilateral submandibular duct ligation, the mean percentage of excessive drooling from all 13 positions and daily activities together declined from 71% at baseline to 15% after 8 weeks (mean difference=55.6, *p*<0.001, 95% CI 46.0–65.3), which increased to 34% 32 weeks posttreatment (mean difference from baseline=37.4, *p*<0.001, 95% CI 31.1–43.7). At both 8 and 32 weeks, bilateral submandibular duct ligation had a greater effect on mean excessive drooling reduction than BoNT-A with a mean difference of –27.4 (*p*<0.001, 95% CI –39.8 to –15.0) and –29.8 (*p*<0.001, 95% CI –37.7 to –21.9) respectively.

Daily care

Baseline values for BoNT-A and bilateral submandibular duct ligation were equal (*p*>0.05) in all three conditions. Both BoNT-A and bilateral submandibular duct ligation decreased the amount of hourly wiping after 8 and 32 weeks but bilateral submandibular duct ligation had a greater effect than BoNT-A at follow-up (mean difference=4.1, *F*[1,51]=8.660, *p*=0.002; 95% CI 1.5–6.7; Fig. 2).

The caregivers of children treated with BoNT-A encouraged their children to swallow a mean of 2.3 times per hour at baseline. Hourly encouragement to swallow decreased non-significantly to 1.8 times per hour after 8 weeks (*p*=0.44, 95% CI –0.8 to 1.8) and showed no further change from 8 to 32 weeks (*p*=0.96, 95% CI –1.1 to 1.0). After bilateral submandibular duct ligation, the hourly encouragement to swallow decreased from 3.6 to 1.6 (*p*=0.009, 95% CI 0.5–3.6) at 8 weeks and to 1.7 per hour (*p*=0.027, 95% CI 0.2–3.6) after 32 weeks, which was not significantly different from BoNT-A (mean difference=0.17, *F*[1,51]=0.267 *p*=0.655; 95% CI –0.6 to 0.9; Fig. 2).

Bilateral submandibular duct ligation reduced the mean number of bib or shawl changes for the collection of saliva from 6 to 4.2 times a day after 8 weeks (*p*=0.05, 95% CI 0.0–3.5) and to three times a day 32 weeks after treatment (*p*=0.039, 95% CI 0.2–5.7). BoNT-A did not significantly change the mean number of bib or shawl changes after 8 and 32 weeks. The difference in reduction induced by bilateral submandibular duct ligation compared to BoNT-A was not significant (mean difference=0.63, *F*[1,51]=0.411, *p*=0.516; 95% CI –1.3 to 2.5).

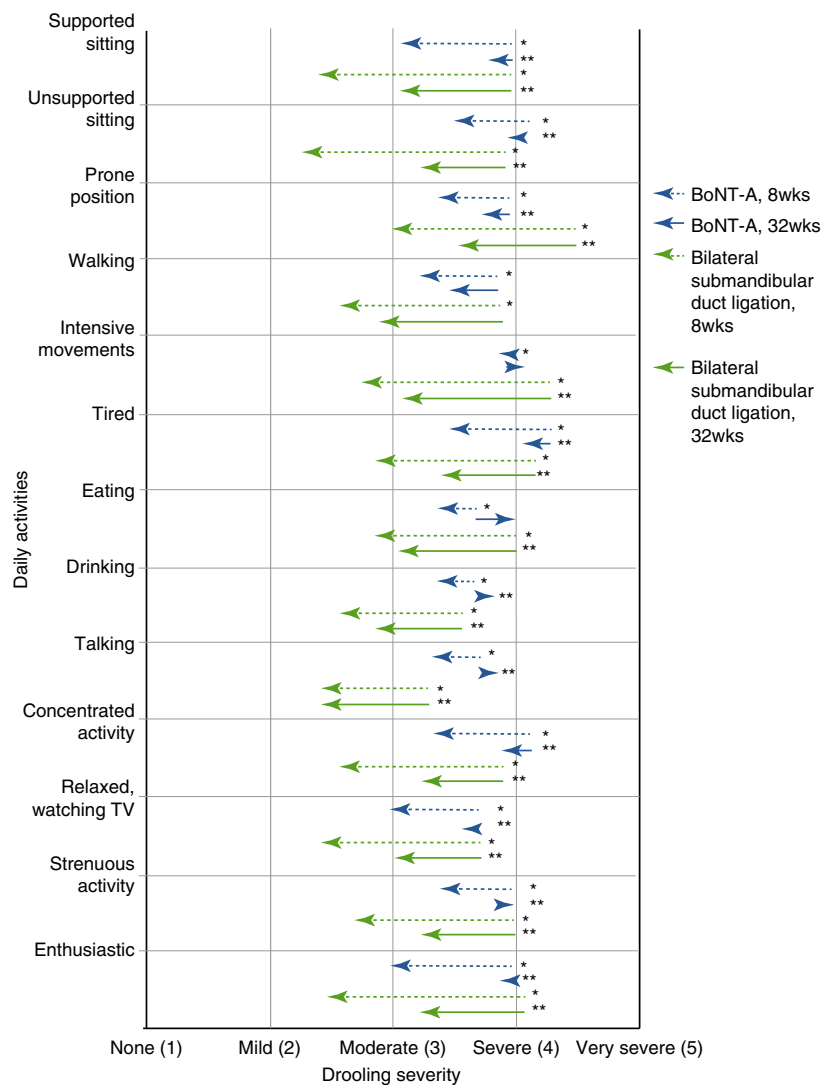


Figure 1: Median reduction in drooling severity 8 and 32 weeks after treatment. *Statistical significance between baseline and 8-weeks follow-up ($p < 0.05$); **statistical significance between baseline and 32-weeks follow-up ($p < 0.05$). BoNT-A, botulinum neurotoxin A.

Damage to electronic devices and/or furniture

Damage to communication aids, electronic communication devices, computers, tablets, and/or audio equipment caused by drooling was reported by 23% (6 of 26) of caregivers before BoNT-A administration. Eight weeks after, this rate dropped to 19% (5 of 26) while 32 weeks after injection 39% (10 of 26) of caregivers reported damage. The caregivers of children treated with bilateral submandibular duct ligation noticed a significant reduction in damage to electronic devices from 30% (8 of 27) at baseline to 11% (3 of 27) 8 weeks after surgery, which remained 11% 32 weeks after treatment. The difference in damage reduction compared to BoNT-A was statistically significant after 32 weeks ($p = 0.032$, $B = 1.77$, 95% CI 1.2–29.7).

Drooling causing damage to floors and/or furniture was reported by 27% (7 of 26) of caregivers before BoNT-A treatment, which diminished to 19% (5 of 26) and 12% (3

of 26) after 8 and 32 weeks respectively. Damage to floors and/or furniture due to drooling in children assigned to bilateral submandibular duct ligation was reported by 15% (4 of 27) of caregivers at baseline. Eight weeks after surgery, no caregivers reported any damage to floors and/or furniture, while after 32 weeks this rate had risen to 11% (3 of 27). A significant difference between the effect of BoNT-A and bilateral submandibular duct ligation on damage to floors and/or furniture was not found.

Social interactions

Drooling appeared to have a negative impact on social interactions as illustrated in Table 2. Both treatments had a positive, yet non-significant influence on social interactions at 8 and 32 weeks after treatment. The impression of caregivers of the child's satisfaction with their social contact with other children and physical appearance during

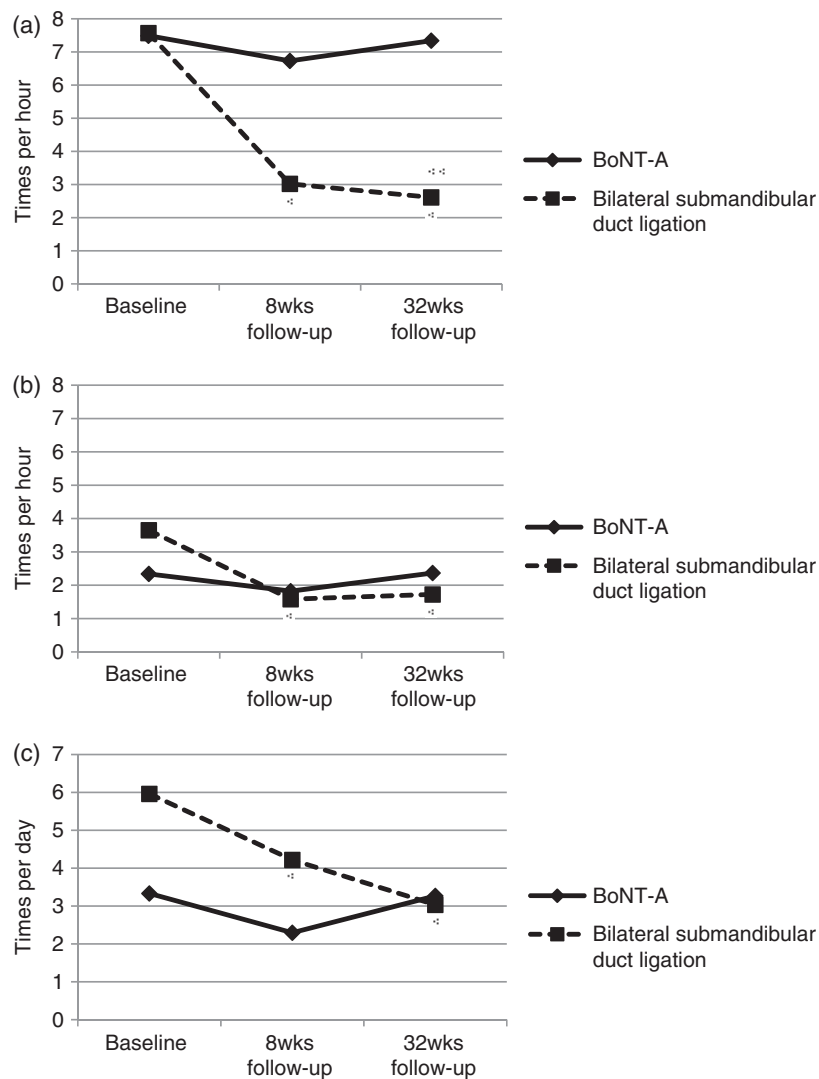


Figure 2: The impact of drooling on daily care. Botulinum neurotoxin A (BoNT-A) ($n=26$); bilateral submandibular duct ligation ($n=27$). (a) Mouth or chin wiped dry. (b) Encouraged to swallow. (c) Bib or shawl replacement. *Statistical significance ($p<0.05$) between baseline and follow-up; **statistical significance between BoNT-A and bilateral submandibular duct ligation ($p<0.05$).

the past 4 weeks improved but did not show a significant difference. The child's satisfaction with their relationships within the family as perceived by their caregivers improved by 17.6 points (mean difference=17.6, $p<0.001$, 95% CI 9.0–26.2) 8 weeks after bilateral submandibular duct ligation and by 10.5 points 32 weeks after bilateral submandibular duct ligation (mean difference=10.5, $p=0.015$, 95% CI –1.9 to –0.2). Likewise, the child's satisfaction with life in general improved after bilateral submandibular duct ligation by 17.6 (mean difference=17.6, $p<0.001$, 95% CI 9.7–25.6) and 12.5 ($p=0.003$, 95% CI 4.2–20.7) points respectively on the 0 to 100 visual analogue scale after 8 and 32 weeks. After BoNT-A, there was no significant improvement at either 8 or 32 weeks. A significant difference between bilateral submandibular duct ligation and BoNT-A was not found.

Self-esteem

To obtain an impression of the occurrence and change in emotional reactions, caregivers were asked whether their child overtly expressed any positive and/or negative feelings about their physical appearance and social acceptance by peers and adults. Eleven children treated with BoNT-A and 12 children in the bilateral submandibular duct ligation group had an estimated developmental age >4 years and were analysed. Overtly negative reactions about physical appearance because of drooling were expressed by 27% (3 of 11) of children and adolescents before BoNT-A and by 8% (1 of 12) before bilateral submandibular duct ligation. Both BoNT-A and bilateral submandibular duct ligation reduced this to 0% at the 32-week follow-up. Similar results were achieved regarding acceptance by adults; 26% and 10% of children and adolescents expressed negative

Table 2: The social consequences of drooling

	BoNT-A (n=26)			Bilateral submandibular duct ligation (n=27)		
	Baseline	8 weeks	32 weeks	Baseline	8 weeks	32 weeks
Avoided by other children						
Yes	14 (54.8)	11 (41.9)	10 (36.3)	15 (56.9)	8 (29.8)	11 (42.0)
Yes, main reason drooling	12 (82.5)	6 (58.7)	7 (76.2)	11 (72.0)	1 (14.9)	8 (66.5)
Avoided by adults						
Yes	8 (31.2)	5 (20.8)	8 (32.1)	10 (38.5)	6 (21.7)	9 (32.4)
Yes, main reason drooling	6 (71.6)	5 (100)	6 (76.0)	8 (73.1)	2 (40.2)	5 (52.6)
Underestimation of mental ability						
Yes	13 (50.6)	13 (51.5)	13 (48.1)	12 (45.7)	12 (43.1)	11 (40.2)
Yes, main reason drooling	5 (37.3)	6 (43.7)	6 (50.4)	7 (58.7)	3 (26.6)	5 (43.3)

Data are n (%). BoNT-A, botulinum neurotoxin A.

reactions because of drooling at baseline for BoNT-A and bilateral submandibular duct ligation respectively. At the 32-week follow-up, children and adolescents did not express any negative reactions because of drooling in both treatment arms. Negative reactions (caused by drooling) by peers were present in 16% of children before BoNT-A and in 18% of children before bilateral submandibular duct ligation. After 32 weeks, this was 30% in the children and adolescents treated with BoNT-A and 0% after bilateral submandibular duct ligation. Statistical analyses regarding emotional reactions were not performed due to the relatively limited numbers.

Adverse events and postoperative complaints

There were more adverse events after bilateral submandibular duct ligation than BoNT-A (40.7% vs 19.2%). The total number of days with postoperative issues was significantly greater after bilateral submandibular duct ligation compared to BoNT-A (9.6d vs 3.9d).⁶

DISCUSSION

This RCT aimed to evaluate and compare the effect of BoNT-A and bilateral submandibular duct ligation on drooling severity in 13 specific positions and daily activities and the impact of drooling on well-being in children and adolescents with neurodevelopmental disorders. Both BoNT-A and bilateral submandibular duct ligation had a positive effect on drooling severity, reducing daily care, decreasing material damage to floors and/or furniture, and improving social interactions. However, submandibular duct ligation was significantly more effective in reducing drooling in the short- (8wks) and medium-term (32wks), making daily care less demanding by reducing the amount of hourly saliva wiping and reducing damage to electronic devices when compared to BoNT-A. Additionally, bilateral submandibular duct ligation – in contrast to BoNT-A – improved the child's satisfaction regarding their relationships within the family and with life in general, having a significantly higher impact on these aspects of well-being in these children and their caregivers.

The reduced effect of BoNT-A injections after 32 weeks was expected since it naturally lasts for a median of

22 weeks.^{4,7,19} However, a prolonged effect of BoNT-A on several domains, although not significant, was experienced at 32 weeks by several participants, which is in line with the observation of a continued effect by Scheffer et al.¹⁹ up to 1 year after injection in a handful of children. Despite this prolonged effect in some participants and the expected effect of BoNT-A at 8 weeks, bilateral submandibular duct ligation had a higher impact on several aspects of well-being in both the short- and medium-term.

Even though both BoNT-A and bilateral submandibular duct ligation were effective in reducing drooling,^{6-8,19,20} the question remains as to how to define a clinically relevant outcome since occasional drooling may still be stigmatizing and burdensome. To many patients and caregivers, the effect of treatment is determined by a reduction in drooling frequency and severity, changes in how it impacts daily life and care, and improvement in well-being and quality of life.²¹ To our knowledge, these factors have not been combined in a randomized controlled setting for BoNT-A and bilateral submandibular duct ligation before.

The effect of BoNT-A and bilateral submandibular duct ligation on the impact of drooling corresponds to a previously published objective effect in this RCT where both treatments were effective but response to treatment after bilateral submandibular duct ligation was higher after 8 (mean difference=35.1%, 95% CI 23.6–46.6) and 32 weeks (mean difference=36.1%, 95% CI 18.1–54.1) than the response to BoNT-A.⁶ Although both treatments improved the well-being of these children, this study, like others, also confirmed some loss of gain between 8 and 32 weeks after both bilateral submandibular duct ligation and BoNT-A.^{6,22-24} Additionally, it highlighted more adverse events and significantly more complaints after bilateral submandibular duct ligation compared to BoNT-A.⁶ The slightly greater risk for complications and morbidity seen after bilateral submandibular duct ligation did not outweigh the impact on the well-being of these children since there were higher scores on most aspects of the questionnaire after bilateral submandibular duct ligation. This might be explained by the relatively mild and temporary complications and adverse events after bilateral

submandibular duct ligation. Namely, there were no long-lasting inconveniences; all adverse events lasted <6 weeks, complaints lasted for a mean of 10 days (range 1–14d, SD 3.9d) post-bilateral submandibular duct ligation, and there was no indication for surgical reintervention.

Previous studies used the Drooling Impact Scale (DIS) to evaluate drooling-related quality of life after BoNT-A.^{25,26} The DIS is a validated quality of life questionnaire for drooling. Reid et al.²⁵ reported a reduction in drooling (-27.5 , $p<0.001$) and improvement in quality of life in children 1 month after salivary gland BoNT-A injections ($n=24$) compared to children in a control group ($n=23$), which corresponds to the findings in this article. Chanu et al.²⁷ assessed the benefit in quality of life with the Glasgow Children's Benefit Inventory 3 months after combined submandibular and parotid duct ligation.²⁷ In this study, a mean Glasgow Children's Benefit Inventory score of $+36.15$ on a scale from -100 (maximum harm) to $+100$ (maximum benefit) was recorded. Even though this general scale did not specifically address the consequences of drooling, diminished drooling was shown to have a major impact on general well-being. However, the improvement in well-being is in line with the findings in the current study.

The data on the effect of BoNT-A and bilateral submandibular duct ligation on the impact of well-being in children with severe drooling collected prospectively in a randomized controlled setting are a major strength of this study. However, there are some potential limitations that need to be addressed. First, there were missing questionnaires and values that might potentially lead to biased results. Multiple imputation was used to adjust for any influencing factors. Second, the questionnaire used in the current study was not validated, unlike the DIS, which was introduced in 2010.²⁵ However, previous research has proven the questionnaire to be sensitive to change over time, which was the main interest in this study.^{2,16–18} Besides, unlike the DIS, the questionnaire also evaluates social and emotional consequences in more detail and quantifies the severity of drooling in multiple positions and daily activities. Nonetheless, having at least a baseline DIS to compare the results to other studies would have improved the current study. Future research should validate the questionnaire used in the current study and assess inter- and intra-responder variability. Third, despite randomization, baseline drooling in several positions and daily activities was not equal between the BoNT-A and bilateral submandibular duct ligation groups. During supported sitting, unsupported sitting, concentrated activity, and strenuous activity, the mean percentage of excessive drooling was significantly higher in children treated with BoNT-A. However, the mean decrease in drooling severity from baseline to 32 weeks after treatment was significantly higher in children treated with bilateral submandibular duct ligation compared to those treated with BoNT-A in all positions and daily activities, suggesting no major influence of the unequal baseline values.

Another limitation of this study is the fact that questionnaires were filled out before inclusion, possibly leading to an exaggeration of complaints to receive treatment. Although wiping and encouragement to swallow might be non-specific for the degree of drooling, both outcomes were included because we felt that they gave an insight into perceived daily care. Moreover, there was no blinding for treatment allocation for patients and caregivers since sham surgery is considered unethical; this may have led to assessment bias in caregivers favouring one of the two treatments.

Future research should consider using a cross-over design to compare treatment within participants, where patients would receive surgery after BoNT-A. Additionally, the questionnaires were not always filled out by the same caregiver. The limited follow-up time is another limitation since reduction in drooling and impact on daily life after bilateral submandibular duct ligation seemed to fade slightly from 8 to 32 weeks of follow-up. Future research should determine the specific long-term effects of bilateral submandibular duct ligation, drooling-related well-being, and quality of life in a larger patient population.

CONCLUSION

Previous literature illustrated that bilateral submandibular duct ligation is a more effective treatment for drooling than BoNT-A but carries a slightly greater risk of complications and morbidity.⁵ This RCT demonstrated a positive effect on the well-being of children, adolescents, and their caregivers through a reduction in drooling severity, daily care, an improvement in social interactions, and higher self-esteem by both BoNT-A and bilateral submandibular duct ligation. Even though there is a greater risk of complications and morbidity after bilateral submandibular duct ligation, it is significantly more effective than BoNT-A with regard to reducing the amount of daily care; damage to electronic devices, floors, and/or furniture; and positive changes in social interactions.

Therefore, bilateral submandibular duct ligation could be considered when, for various reasons, BoNT-A is no longer preferred and when submandibular gland extirpation or submandibular duct relocation are rejected or contraindicated. In our clinic, systemic anticholinergics are currently only considered in case of an unsatisfactory result from or contraindications to BoNT-A or surgery. Future research should focus on the cost-effectiveness, long-term effect on drooling severity, and related impact of bilateral submandibular duct ligation compared with alternative surgery to determine the role of bilateral submandibular duct ligation in current drooling treatment strategies.

ACKNOWLEDGEMENTS

We thank Peter Jongerius, rehabilitation specialist, who performed all the BoNT-A injections, Laura Rodwell, for her contribution to the statistical analysis, and Corrie Erasmus for her contribution to the establishment and development of the trial. This study was supported by Johanna Kinderfonds, Arnhem, the Netherlands, Phelps

Stichting voor spastici, Bussum, the Netherlands and Stichting Rotterdams Kinderrevalidatie Fonds Adriaanstichting, Rotterdam, the Netherlands. The authors have stated they had no interests that might be perceived as posing a conflict or bias.

DATA AVAILABILITY STATEMENT

De-identified individual participant data (including data dictionaries) can be made available, along with the study protocols, statistical analysis plan, and informed consent form.

REFERENCES

- Speyer R, Cordier R, Kim J-H, Cocks N, Michou E, Wilkes-Gillan S. Prevalence of drooling, swallowing, and feeding problems in cerebral palsy across the lifespan: a systematic review and meta-analyses. *Dev Med Child Neurol* 2019; **61**: 1249–58.
- van der Burg J, Jongerius P, van Limbeek J, van Hulst K, Rotteveel J. Drooling in children with cerebral palsy: a qualitative method to evaluate parental perceptions of its impact on daily life, social interaction, and self-esteem. *Int J Rehabil Res* 2006; **29**: 179–82.
- Hockstein NG, Samadi DS, Gendron K, Handler SD. Sialorrhea: a management challenge. *Am Fam Physician* 2004; **69**: 2628–34.
- Meningaud J-P, Pitak-Arnop P, Chikhani L, Bertrand J-C. Drooling of saliva: a review of the etiology and management options. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; **101**: 48–57.
- Erasmus CE, van Hulst K, Rotteveel JJ, Willemsen MAAP, Jongerius PH. Clinical practice: swallowing problems in cerebral palsy. *Eur J Pediatr* 2012; **171**: 409–14.
- Bekkers S, Delsing CP, Kok SE, et al. Randomized controlled trial comparing botulinum vs surgery for drooling in neurodisabilities. *Neurology* 2019; **92**: e1195–204.
- Erasmus CE, van Hulst K, Rotteveel JJ, Willemsen MAAP, Jongerius PH. Clinical practice: swallowing problems in cerebral palsy. *Eur J Pediatr* 2012; **171**: 409–14.
- Scheffer ART, Bosch KJAM, van Hulst K, van den Hoogen FJA. Salivary duct ligation for anterior and posterior drooling: our experience in twenty-one children. *Clin Otolaryngol* 2013; **38**: 425–9.
- Kok SE, Erasmus CE, Scheffer ART, van Hulst K, Rovers MM, van den Hoogen FJA. Effectiveness of submandibular duct relocation in 91 children with excessive drooling: a prospective cohort study. *Clin Otolaryngol* 2018; **43**: 1471–7.
- El-Hakim H, Richards S, Thevasagayam MS. Major salivary duct clipping for control problems in developmentally challenged children. *Arch Otolaryngol Head Neck Surg* 2008; **134**: 470–4.
- Klem C, Mair EA. Four-duct ligation: a simple and effective treatment for chronic aspiration from sialorrhea. *Arch Otolaryngol Head Neck Surg* 1999; **125**: 796–800.
- Delsing CPA, Viergever T, Honings J, van den Hoogen FJA. Bilateral transcervical submandibular gland excision for drooling: a study of the mature scar and long-term effects. *Eur J Paediatr Neurol* 2016; **20**: 738–44.
- Martin TJ, Conley SF. Long-term efficacy of intra-oral surgery for sialorrhea. *Otolaryngol Head Neck Surg* 2007; **137**: 54–8.
- Bekkers S, van Ulsen KJ, Addang EMM, Scheffer ART, van den Hoogen FJA. Cost-effectiveness of botulinum neurotoxin A versus surgery for drooling: a randomized clinical trial. *Dev Med Child Neurol* 2020; **62**: 1302–8.
- Thomas-Stonell N, Greenberg J. Three treatment approaches and clinical factors in the reduction of drooling. *Dysphagia* 1988; **3**: 73–8.
- 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.
- Van der Burg JJW, Jongerius PH, Van Hulst K, Van Limbeek J, Rotteveel JJ. Drooling in children with cerebral palsy: effect of salivary flow reduction on daily life and care. *Dev Med Child Neurol* 2006; **48**: 103–7.
- Kok SE, van der Burg JJW, van Hulst K, Erasmus CE, van den Hoogen FJA. The impact of submandibular duct relocation on drooling and the well-being of children with neurodevelopmental disabilities. *Int J Pediatr Otorhinolaryngol* 2016; **88**: 173–8.
- Scheffer ART, Erasmus C, van Hulst K, van Limbeek J, Jongerius PH, van den Hoogen FJA. Efficacy and duration of botulinum toxin treatment for drooling in 131 children. *Arch Otolaryngol Head Neck Surg* 2010; **136**: 873–7.
- 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**: 123–8.
- Blasco P. The treatment of drooling. *Dev Med Child Neurol* 2010; **52**: 984.
- Bekkers S, Pruijn IMJ, Van Hulst K, et al. Submandibular duct ligation after botulinum neurotoxin A treatment of drooling in children with cerebral palsy. *Dev Med Child Neurol* 2020; **62**: 861–7.
- Bekkers S, van Hulst K, Erasmus CE, Delsing CP, Scheffer ART, van den Hoogen FJA. An evaluation of predictors for success of two-duct ligation for drooling in neurodisabilities. *J Neurol* 2020; **267**: 1508–15.
- Delsing CPA, Bekkers S, van Hulst K, Erasmus CE, van den Hoogen FJA. Unsuccessful submandibular duct surgery for anterior drooling: surgical failure or parotid gland salivation? *Int J Pediatr Otorhinolaryngol* 2019; **123**: 132–7.
- Reid SM, Johnson HM, Reddihough DS. The Drooling Impact Scale: a measure of the impact of drooling in children with developmental disabilities. *Dev Med Child Neurol* 2010; **52**: e23–8.
- Parr JR, Todhunter E, Pennington L, et al. Drooling Reduction Intervention randomised trial (DRI): comparing the efficacy and acceptability of hyoscine patches and glycopyrronium liquid on drooling in children with neurodisability. *Arch Dis Child* 2018; **103**: 371–6.
- Chanu NP, Sahni JK, Aneja S, Naglot S. Four-duct ligation in children with drooling. *Am J Otolaryngol* 2012; **33**: 604–7.

Data will be made available upon publication to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal. Proposals should be submitted to Stijn.bekkers@radboudumc.nl.

SUPPORTING INFORMATION

The following additional material may be found online:

Figure S1: Consort flow diagram.

Appendix S1: Drooling questionnaire.