

# Submandibular duct ligation after botulinum neurotoxin A treatment of drooling in children with cerebral palsy

STIJN BEKKERS<sup>1</sup>  | INEKE M J PRUIJN<sup>1</sup>  | KAREN VAN HULST<sup>2</sup>  | CORINNE P DELSING<sup>1</sup>  |  
CORRIE E ERASMUS<sup>3</sup> | ARTHUR R T SCHEFFER<sup>1</sup> | FRANK J A VAN DEN HOOGEN<sup>1</sup>

**1** Department of Otorhinolaryngology and Head and Neck Surgery, Radboud University Medical Center, Nijmegen; **2** Department of Rehabilitation, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen; **3** Department of Paediatric Neurology, Donders Center for Neuroscience, Radboud University Medical Center, Nijmegen, the Netherlands.

Correspondence to Ineke M J Pruijn, Radboud University Medical Center, Philips van Leijdenlaan 15 (route 377), Nijmegen, Postbus 9101, 6500 HB, the Netherlands.  
E-mail: Ineke.Pruijn@radboudumc.nl

## PUBLICATION DATA

Accepted for publication 28th January 2020.

Published online 9th March 2020.

## ABBREVIATIONS

SMDR Submandibular duct relocation  
VAS Visual Analogue Scale

**AIM** To assess: (1) the effect on drooling of bilateral submandibular duct ligation as surgical therapy after the administration of submandibular botulinum neurotoxin A (BoNT-A) for excessive drooling and (2) the predictive value of treatment success with BoNT-A on treatment success after bilateral submandibular duct ligation.

**METHOD** This was a within-participant retrospective observational study in which 29 children with severe drooling (15 males, 14 females) received BoNT-A treatment at a mean age of 9 years 6 months (SD 2y 5mo), followed by bilateral submandibular duct ligation at a mean age of 10 years 11 months (SD 2y 4mo). Fifteen children were diagnosed with cerebral palsy (CP), with 12 children classified in Gross Motor Function Classification System levels IV and V. The 14 children without CP had non-progressive developmental disorders. The primary drooling severity outcomes were the Visual Analogue Scale (VAS; subjective assessment) and drooling quotient (objective assessment). Measurements were taken before each intervention and again at 8 and 32 weeks.

**RESULTS** The VAS was significantly lower after bilateral submandibular duct ligation at follow-up compared to BoNT-A treatment (mean difference  $-33$ ,  $p \leq 0.001$ ; 95% confidence interval [CI]  $-43.3$  to  $-22.9$ ). The mean drooling quotient did not significantly differ between BoNT-A treatment and bilateral submandibular duct ligation at follow-up ( $3.3$ ,  $p = 0.457$ ; 95% CI  $-4.35$  to  $9.62$ ) or between 8 and 32 weeks ( $4.7$ ,  $p = 0.188$ ; 95% CI  $-2.31$  to  $11.65$ ).

**INTERPRETATION** BoNT-A treatment and bilateral submandibular duct ligation are both effective treatment modalities for drooling. At 32-week follow-up, subjective drooling severity after bilateral submandibular duct ligation was significantly lower compared to previous BoNT-A injections in participants. However, treatment success with BoNT-A is no precursor to achieving success with bilateral submandibular duct ligation.

Drooling is the unintentional loss of saliva from the mouth; it is considered pathological after the age of 4 years. In many children and adolescents with cerebral palsy (CP) or any other non-progressive developmental disorder, drooling is a major burden. Approximately 40% of children with CP experience drooling, which has high physical and social-emotional morbidity and a major impact on their daily lives.<sup>1,2</sup> The treatment of drooling is a clinical challenge since not all treatment options are well suited to every child in this vulnerable patient population.

Submandibular glands are responsible for 70% of total saliva production in the unstimulated state. Therefore, at our institution, submandibular glands are the primary aim for interventional therapy. Botulinum neurotoxin A (BoNT-A) injections into the submandibular glands are frequently used to treat drooling when more conservative

treatments such as oral or behavioural therapy and anticholinergic medications have failed to achieve satisfactory results.<sup>3</sup> BoNT-A has been shown to be effective<sup>4,5</sup> and is minimally invasive. Adverse events are usually minor and include mainly changes in oral-motor function.<sup>6</sup> However, the effects of BoNT-A treatment are by nature temporary, lasting for only several months; thus, repeated injections under general anaesthesia are needed to maintain the effects of BoNT-A. This produces an increased burden with the risks of repetitive anaesthesia and potential adverse effects, which ultimately results in patients and carers opting for longer-lasting treatment modalities.

During the past decades, several surgical procedures have been suggested to achieve longer-lasting results. Submandibular duct relocation (SMDR), where the submandibular ducts are relocated from the anterior oral

cavity to the base of the tongue, is currently one of the most effective surgical procedures.<sup>7–12</sup> The main downside of SMDR is perioperative morbidity, which requires hospitalization for multiple days, including a 1-night admission to the intensive care unit for assisted breathing due to the risk of airway obstruction as a result of postoperative swelling of the mouth floor. Another potential, although smaller risk, is damage to the lingual nerve. In addition, SMDR is unsuitable in children with posterior drooling (saliva aspiration). Bilateral submandibular gland excision is another surgical procedure that can provide a longer-lasting solution to drooling. Potential disadvantages include a small risk of damage to the lingual, hypoglossal, and mandibular branches of the facial nerve. Additionally, an external incision is required. This leaves a scar that is generally cosmetically acceptable to children and their caregivers.<sup>13</sup>

In the recent decade, bilateral submandibular duct ligation has arisen as a potential minimally invasive surgical procedure to treat drooling. In contrast to SMDR and bilateral submandibular gland excision, bilateral submandibular duct ligation is performed as part of day care with a shorter surgery that is safe and effective.<sup>14–16</sup> However, due to a lack of comparative studies, the relevance of bilateral submandibular duct ligation is yet to be determined among the range of surgical treatment options open to families who choose not to continue with repeated BoNT-A injections or patients in whom BoNT-A is not effective. Since both treatment modalities aim to reduce submandibular salivary flow, we might expect treatment success after submandibular BoNT-A injections to have a predictive value with regard to treatment success derived from bilateral submandibular duct ligation.

This within-participant retrospective observational study aimed to compare subjective and objective drooling severity after bilateral submandibular duct ligation in children with severe drooling first treated with BoNT-A and evaluate if BoNT-A treatment success is a predictor for treatment success after bilateral submandibular duct ligation.

## METHOD

### Study design

We retrospectively identified children who had first been treated with bilateral submandibular BoNT-A injections and who subsequently underwent bilateral submandibular duct ligation surgery. The study design, which reflects clinical practice, compared the effect of bilateral submandibular duct ligation to BoNT-A treatment in each participant, thus reducing confounding factors and increasing reliability and statistical power in a heterogeneous population of children with CP and other non-progressive developmental disorders. Regarding multiple BoNT-A procedures preceding bilateral submandibular duct ligation, only data from the latest BoNT-A injection was used for analysis. Original standardized assessments were made by a specialized speech and language therapist before each treatment and again at 8 and 32 weeks after treatment.

### What this paper adds

- Bilateral submandibular duct ligation is an effective therapy for drooling after treatment with botulinum neurotoxin A (BoNT-A).
- Treatment success with BoNT-A is not a predictor of successful therapy with bilateral submandibular duct ligation.

### Participants

All children eligible for participation visited the Multidisciplinary Saliva Control Center of the Radboud University Medical Center, Nijmegen, the Netherlands, between December 2005 and October 2017. The cohort was evaluated retrospectively. Participants diagnosed with CP or a non-progressive developmental disorder accompanied by severe drooling, who chose to discontinue repeated BoNT-A injections, were included. Reasons given for surgery preference included experiencing inadequate drooling control, BoNT-A side effects, or the desire for a long-term solution. Exclusion criteria included: concurrent alternative treatment for drooling; fewer than 6 months or more than 5 years between the last BoNT-A injection and bilateral submandibular duct ligation; more than one missing follow-up measurement; or a missing baseline measurement (Table 1). The research was performed in accordance with national and international ethical standards. The regional review board decided that specific ethical permission for this observational study was not required. Informed consent by caregivers was provided before each intervention.

### Procedures

All participants had previously undergone BoNT-A injections followed by surgery at least 6 months later. Both procedures were performed as part of day care. BoNT-A (Botox; Allergan, Dublin, Republic of Ireland) was administered under general anaesthesia, fractioning 1ml over two or three sites throughout the submandibular gland using a Spinocan needle and ultrasound guidance.<sup>6</sup>

Surgery was also performed under general anaesthesia. After the floor of the mouth was infiltrated with local

**Table 1:** Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age 4–18y	Simultaneous medical treatment for drooling
Diagnosed with cerebral palsy or non-progressive developmental disorders	Simultaneous use of benzodiazepines
Severe drooling (Teacher Drooling Scale $\geq 3$ ) <sup>a</sup>	Treatment with BoNT-A $\leq 6$ mo before surgery
At least one treatment with BoNT-A in submandibular glands before bilateral submandibular duct ligation	Missing baseline value or $>1$ subsequent missing measurement
Treated with bilateral submandibular duct ligation	More than 5y between BoNT-A and bilateral submandibular duct ligation

<sup>a</sup>Teacher Drooling Scale: 1, no drooling; 2, infrequent drooling, small amount; 3, occasional drooling, on and off all day; 4, frequent drooling, but not profuse; 5, constant drooling, always wet. BoNT-A, botulinum neurotoxin A.

anaesthetic and adrenaline, the submandibular ducts were identified through a midline incision parallel to the lingual frenulum. After identification, the duct was freed for 1 to 2 cm. Initially, the submandibular ducts were ligated with non-resorbable 3-0 polyester sutures ( $n=3$ ). From August 2008, metal vascular clips were used as substitutes for ligation ( $n=26$ ). Vicryl 3-0 intraoral resorbable sutures were used to close the floor of the mouth. Antibiotics (combination of amoxicillin and clavulanate potassium) were prescribed for 7 days and diclofenac for 5 days postoperatively.

### Outcome measures

Drooling was assessed subjectively by caretakers using the Visual Analogue Scale (VAS) for severity of drooling during the 2 weeks before assessment. The assigned drooling score ranged from 0 (no drooling) to 100 (severe drooling) at all visits.

Drooling severity was evaluated objectively using the validated, semi-quantitative drooling quotient, a method where the presence of new saliva on the lip or chin is directly observed every 15 seconds and recorded by a specialized speech and language therapist for 5 minutes.<sup>17</sup> Participants were evaluated at least 1 hour after a meal, while awake and sitting up straight. To personalize the evaluation of treatment success, this was defined as a  $\geq 50\%$  reduction in VAS and/or drooling quotient from baseline.<sup>16</sup> Other research groups have used similar definitions of treatment success or relied on a  $\geq 2SD$  reduction in either VAS and/or drooling quotient.

### Statistical analysis

Data were analysed with SPSS v22.0 for Windows (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize patient characteristics. Continuous variables were analysed with paired and unpaired *t*-tests. If the assumption of normally distributed data was violated according to the Shapiro–Wilk test, continuous variables were analysed with the Wilcoxon signed-rank and Mann–Whitney *U* tests. Evaluation of treatment response over time was performed using a linear mixed model with change in the VAS as the dependent variable and treatment and visits as the fixed factors. The predictive value of BoNT-A treatment success after 8 and 32 weeks on treatment success 32 weeks after bilateral submandibular duct ligation was tested with a  $\chi^2$  test.

To evaluate a potential selection bias for the inclusion of only poor responders to BoNT-A or differences in patient characteristics, we compared the participants in our study to a cohort of 232 children who received a total of 407 BoNT-A injections at our centre between January 2002 and May 2013.<sup>1</sup> Differences in mean VAS and drooling quotient and baseline patient characteristics (i.e. age, epilepsy, intellectual disability, CP diagnosis, Gross Motor Function Classification System level) between the two groups were analysed with Mann–Whitney *U* and  $\chi^2$  tests respectively. Statistical significance was defined as  $p \leq 0.05$

for all statistical analyses; 95% confidence intervals (CIs) were provided for the interpretation of point estimates.

## RESULTS

Of the children in our centre treated with BoNT-A injections for severe drooling, 33 subsequently underwent bilateral submandibular duct ligation and were eligible for inclusion. Two children were excluded due to the concurrent use of benzodiazepines. In one child, treatment success with BoNT-A was not measured because treatment and follow-up took place at another centre; another patient was excluded because the time between BoNT-A treatment and bilateral submandibular duct ligation exceeded 5 years. Fifteen children were diagnosed with CP; the other 14 children had non-progressive developmental disorders either unexplained or mainly as part of a syndrome (e.g. Dandy–Walker, de Grouchy), genetic (e.g. trisomy 1q), or metabolic disorder. The characteristics of the 29 children included in the study (15 males, 14 females) are shown in Table 2.

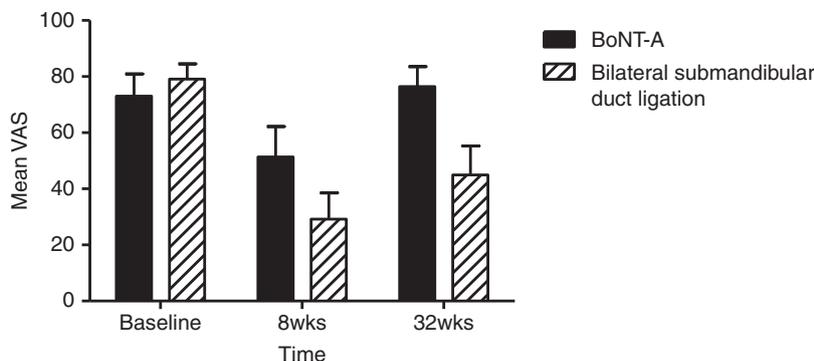
There were no missing data at baseline and no missing VAS scores at follow-up for either intervention. The drooling quotient follow-up rate 8 weeks (mean 8wks 6d; SD 2wks 5d) after BoNT-A injection was 100%. The drooling quotient 32 weeks after BoNT-A injection was not measured in one child, while in another patient the drooling quotient was omitted due to an unreliable measurement (the patient put her hands in her mouth during the measurement); this resulted in a 93.1% follow-up rate (mean 34wks 1d; SD 5wks 4d). There were no missing drooling quotient measurements 8 weeks (mean 8wks 6d; SD 1wks 1d) after bilateral submandibular duct ligation. The drooling quotient follow-up rate 32 weeks after bilateral submandibular duct ligation (mean 34wks 1d; SD 5wks 5d) was 97%; one patient did not attend the appointment due to personal circumstances. However, subjective assessment of this patient was made through a phone call.

The average age at the time of BoNT-A administration was 9 years 6 months (SD 2y 5mo; range 6–15y) and 10 years 11 months (SD 2y 4mo; range 8–16y) at the time of surgery. Postoperative submandibular swelling was seen in all children after bilateral submandibular duct ligation. This was temporary and self-limiting within 2 weeks in all patients. Transient swallowing difficulties were reported by two patients after BoNT-A injection. One child was admitted to hospital with pneumonia after BoNT-A injection and developed another bout of pneumonia after bilateral submandibular duct ligation, which was treated at home. Another child was treated with oral antibiotics for mild pneumonia after bilateral submandibular duct ligation. One child mentioned temporary, self-limiting nasal regurgitation after bilateral submandibular duct ligation. One patient underwent bilateral excision of the ranula, excision of the sublingual glands, and repeated ligation of the submandibular ducts 2 years after the initial bilateral submandibular duct ligation. There were no cases of wound infection.

**Table 2:** Baseline patient characteristics

	Male (n=15)	Female (n=14)	Total (n=29)
Mean (SD) age at intervention, y:mo			
BoNT-A	9:10 (2:9)	9:3 (2:3)	9:6 (2:5)
Bilateral submandibular duct ligation	11:5 (2:6)	10:6 (2:2)	10:1 (2:4)
Mean (SD) BoNT-A injections before bilateral submandibular duct ligation; range	2.8 (1.7); 1–7	1.7 (1.1); 1–5	2.3 (1.5); 1–7
Drooling, <sup>a</sup> n (%)			
Anterior	9 (60)	6 (42.9)	15 (51.7)
Antero-posterior	6 (40)	8 (57.1)	14 (48.3)
Main diagnosis, n (%)			
Spastic CP	4 (26.7)	3 (21.4)	7 (24.1)
Dyskinetic CP	0 (0)	3 (21.4)	3 (10.3)
Spastic/dyskinetic CP	4 (26.7)	1 (7.1)	5 (17.2)
Other developmental disability <sup>b</sup>	7 (46.7)	7 (50.0)	14 (48.3)
GMFCS level, <sup>c</sup> n (%)			
II	1 (12.5)	1 (14.3)	2 (13.3)
III	1 (12.5)	0 (0)	1 (6.7)
IV	2 (25.0)	5 (71.4)	7 (46.7)
V	4 (50.0)	1 (14.3)	5 (33.3)
Degree of mobility, total group, n (%)			
Ambulant	8 (53.3)	5 (35.7)	13 (44.8)
Non-ambulant	7 (46.7)	9 (64.3)	16 (55.2)
Developmental age, n (%)			
<4y	12 (80.0)	5 (35.7)	17 (58.6)
>4y	3 (20.0)	9 (64.3)	12 (41.4)
Epilepsy, n (%)			
Yes	12 (80.0)	9 (64.3)	21 (72.4)
Controlled	10 (83.3)	9 (100)	19 (90.5)
Intractable	2 (16.7)	0 (0)	2 (9.5)
No	3 (20.0)	5 (35.7)	8 (27.6)

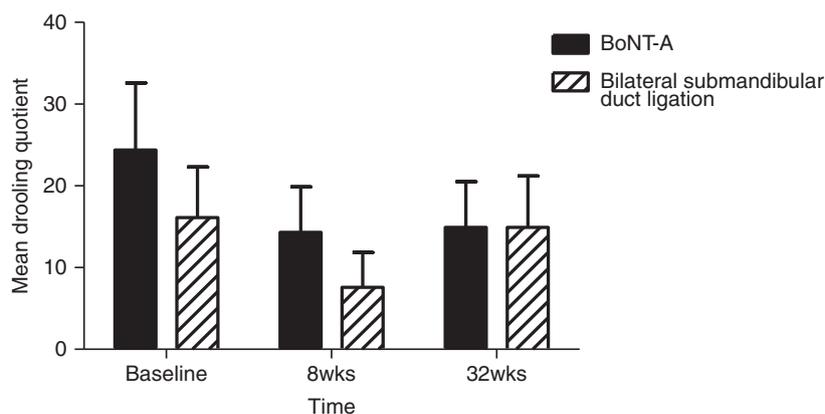
<sup>a</sup>Anterior drooling is the unintentional loss of saliva from the mouth towards the chin. Posterior drooling is the uncontrolled leakage of saliva over the tongue base through the faucial isthmus.<sup>31</sup> Antero-posterior drooling is the coexistence of both anterior and posterior drooling. <sup>b</sup>Other developmental disability: children with unexplained non-progressive developmental disabilities or mainly as part of a syndrome (e.g. Dandy–Walker, de Grouchy), genetic (e.g. trisomy 1q), or metabolic disorder. <sup>c</sup>Score only applies to cerebral palsy (CP; n=15). Gross Motor Function Classification System (GMFCS) level I–III is classified as ambulant. GMFCS level IV and V is classified as non-ambulant. BoNT-A, botulinum neurotoxin A.



**Figure 1:** Mean Visual Analogue Scale (VAS) over time after botulinum neurotoxin A (BoNT-A) and bilateral submandibular duct ligation with 95% confidence intervals.

The linear mixed model showed a significant difference in mean VAS for both BoNT-A and bilateral submandibular duct ligation at follow-up (Fig. 1). VAS was significantly lower 8 weeks after treatment (mean 40.3) compared to 32 weeks after treatment (mean 60.7) (mean difference  $-20.4$ ,  $F[1,113]=16.449$ ,  $p\leq 0.001$ ; 95% CI= $-10.7$  to  $-31.1$ ). Even though both interventions were effective, VAS was significantly lower at follow-up after bilateral

submandibular duct ligation (mean 34) compared to BoNT-A (mean 66) (mean difference  $-33$ ,  $F[1,113]=41.279$ ,  $p\leq 0.001$ ; 95% CI= $-43.3$  to  $-22.9$ ). There was no significant difference in drooling quotient at the 8-week (mean 10.9) and 32-week (mean 14.6) follow-up (mean difference 4.7,  $F[1,106]=1.757$ ,  $p=0.188$ ; 95% CI= $-2.31$  to  $11.65$ ) and no significant difference in drooling quotient scores at follow-up between BoNT-A injection (mean



**Figure 2:** Mean drooling quotient over time after botulinum neurotoxin A (BoNT-A) and bilateral submandibular duct ligation with 95% confidence intervals.

14.6) and bilateral submandibular duct ligation (mean 11.3) (mean difference 3.3,  $F[1,106]=0.558$ ,  $p=0.457$ ; 95% CI=-4.35 to 9.62), as illustrated by Figure 2.

Despite a -7.1 drooling quotient before surgery, this difference was non-significant ( $z$ -score=-1.9,  $p=0.06$ ). The 6.0 VAS baseline before bilateral submandibular duct ligation compared to the VAS before BoNT-A was also non-significant ( $z$ -score=-1.7,  $p=0.094$ ).

With treatment success defined as a  $\geq 50\%$  reduction in VAS and/or drooling quotient from baseline, 20 children showed successful treatment with BoNT-A after 8 weeks and 10 after 32 weeks. Submandibular duct ligation resulted in 24 children treated successfully after 8 weeks; 15 children showed continued treatment success after 32 weeks.

Treatment success 32 weeks after bilateral submandibular duct ligation could not be predicted by BoNT-A treatment success after 8 weeks. Only half of the children successfully treated 8 weeks after BoNT-A (positive predictive value 50%, 95% CI=0.17-3.89) were treated successfully 32 weeks after bilateral submandibular duct ligation. Additionally, an unsuccessful response 8 weeks after BoNT-A treatment was not a predictor for bilateral submandibular duct ligation treatment failure since only 4 out of the 9 (negative predictive value 44%) children treated unsuccessfully 8 weeks after BoNT-A also failed to reach treatment success 32 weeks after bilateral submandibular duct ligation (95% CI=0.17-3.89). Likewise, there was no predictive value of treatment success 32 weeks after BoNT-A and treatment success 32 weeks after bilateral submandibular duct ligation (positive predictive value 40%, 95% CI=0.10-2.31).

Potential selection bias was examined by comparing patient characteristics and response to BoNT-A in these 29 children with the response to 407 BoNT-A treatments for drooling in 232 children treated at our centre between January 2002 and May 2013. Baseline VAS values between the two groups did not differ significantly (73 vs 72.9;  $U=5637$ ,  $p=0.718$ ; 95% CI=0.71-0.73). Likewise, the VAS scores 8 weeks after BoNT-A treatment were closely related (51.3 vs 50.9;  $U=5800$ ,  $p=0.894$ ; 95% CI=0.89-0.90). However, the

VAS scores 32 weeks after BoNT-A treatment were 13 points higher in the children included in this study than the other group of children ( $n=232$ ) treated with BoNT-A (76.5 vs 63.5;  $U=3874$ ,  $p=0.002$ ; 95% CI=0.001-0.003). The baseline drooling quotient scores were comparable (24.4 vs 29.9;  $U=5584$ ,  $p=0.628$ ; 95% CI=0.62-0.64) between the two groups: drooling quotient scores at 8 weeks (14.3 vs 16.5;  $U=5880$ ,  $p=0.973$ ; 95% CI=0.97-0.98); drooling quotient scores at 32 weeks (16 vs 17.9;  $U=5357$ ,  $p=0.826$ ; 95% CI=0.81-0.83) after BoNT-A treatment. Patient characteristics that may influence drooling severity, such as age (9.6 vs 10.2;  $p=0.475$ ; 95% CI=-0.18 to 0.21), epilepsy (72% vs 57%;  $p=0.299$ ; 95% CI=-0.34 to 0.11), developmental age (59% vs 64% <4y;  $p=0.554$ ; 95% CI=-0.25 to 0.14), CP diagnosis (52% vs 66%;  $p=0.145$ ; 95% CI=-0.05 to 0.34), and Gross Motor Function Classification System level  $\geq IV$  (80% vs 84%  $p=0.461$ ; 95% CI=-0.27 to 0.13), did not differ significantly between the children included in this study and the 232 children treated with BoNT-A injections at our centre.

## DISCUSSION

This study evaluated the effect of bilateral submandibular duct ligation after BoNT-A treatment and the predictive value of treatment success after BoNT-A on the treatment success derived from bilateral submandibular duct ligation in children with severe drooling. The findings show that both BoNT-A and bilateral submandibular duct ligation are effective in treating drooling. However, in patients first treated with BoNT-A who later received bilateral submandibular duct ligation, surgery provided a significantly larger and longer-lasting subjective reduction in drooling at 32 weeks follow-up compared to the effect of BoNT-A administered previously. But the difference could not be confirmed objectively (i.e. with the drooling quotient).

Even though both VAS and drooling quotient significantly dropped 8 weeks after bilateral submandibular duct ligation, both increased significantly ( $z$ -score=-3.0,  $p<0.001$  and  $z$ -score=-2.2,  $p=0.001$  respectively) 32 weeks

after bilateral submandibular duct ligation, suggesting recurrence. Although submandibular duct ligation in rats eventually results in salivary gland atrophy and cessation in saliva production,<sup>18</sup> recurrence in the long-term is rather common in surgery such as duct ligation.<sup>14</sup> One of the suggested explanations involves upregulation of the sublingual and minor salivary glands to maintain sufficient saliva, thus preventing xerostomia and promoting dental health. Another theory explains recurrence by the development of alternative salivary pathways.<sup>15</sup> Therefore, future research should focus on recurrence after bilateral submandibular duct ligation in the long-term.

Although not specific to submandibular duct ligation alone, previous studies regarding glandular duct ligation to treat sialorrhea have reported varying success rates from 50% to 81%.<sup>15,19–22</sup> Our success rate of 83% after 8 weeks exceeds these previously reported results for both submandibular and combined duct ligations but is in line with former success rates reported at our centre (88.9%). However, this study involved patients who were included in a previous study conducted at our centre.<sup>16</sup> Therapeutic success 8 weeks after BoNT-A treatment was 69%, which is slightly higher compared to the 46% to 65% success rates reported in other studies carried out at our centre.<sup>4,6,16,23</sup> It must be noted that some authors define therapeutic success by either drooling quotient or VAS or use a combination with a 50% reduction in VAS and/or a 2SD reduction in drooling quotient. Interestingly, our findings suggest that neither BoNT-A treatment success nor treatment failure precludes subsequent treatment response to bilateral submandibular duct ligation. This might be explained by the variable response to BoNT-A treatment across individuals<sup>24</sup> or by a difference in the mechanism of action between BoNT-A and bilateral submandibular duct ligation, even though both treatment strategies aim to reduce salivary flow from the submandibular glands.

Adverse effects occurred in 10.3% of children after BoNT-A injection, which is lower than the 33% reported adverse effects mentioned in a recent study on submandibular BoNT-A injections.<sup>6</sup> There are several explanations for this difference. First, van Hulst et al.<sup>6</sup> encouraged caregivers to contact the speech and language therapist for advice if any change in oral-motor function occurred during the first 8 weeks. Second, caregivers were conceivably more attentive to changes after BoNT-A treatment since children in the study by van Hulst et al.<sup>6</sup> received submandibular BoNT-A injections for the first time whereas children in our study received a mean of 2.3 BoNT-A injections before bilateral submandibular duct ligation. Adverse events after bilateral submandibular duct ligation occurred in four children (13.8%); this broadly corresponds to the 19% adverse events reported by Scheffer et al.<sup>14</sup>

A strength of the current study is the within-participant comparison of two management strategies to treat drooling. Children with CP and neurodevelopmental disabilities form a heterogeneous population where there is much variability, not solely in the physical and mental expression of

the condition, but also in response to treatment since response to BoNT-A treatment varies with each individual. The chosen observational design enables within-participant comparison of both BoNT-A injection and bilateral submandibular duct ligation; therefore, it reduces the influence of covariates and strengthens study reliability.

However, this study also has several limitations. There is a strong potential for selection bias since one of the main reasons to terminate BoNT-A injections is an inadequate effect, which is reflected by the relatively high subjective VAS scores compared to the objective drooling quotient scores.<sup>25</sup> It could be argued that only poor responders to BoNT-A treatment were included in this study. However, although VAS scores at 32 weeks were significantly higher in this study compared to the larger cohort of patients undergoing BoNT-A ( $n=232$ ), there was a significant decrease in the objective outcome (drooling quotient) after 32 weeks, which is equal to that recorded for the larger cohort of patients treated with BoNT-A. This suggests that there was an adequate objective reduction in drooling without an equal subjective reduction, thereby making it unlikely that only poor responders to a reduction in drooling were included. The VAS may be influenced by dissatisfaction caused by former experiences with BoNT-A treatment, any benefits not outweighing the related burden of the BoNT-A procedure, or any results not meeting preset expectations. Additionally, wishing for a permanent solution might consciously or unconsciously lead to a higher VAS score. Another concern in this study is the 6-month washout period between BoNT-A injection and bilateral submandibular duct ligation. Even though BoNT-A treatment is thought to have a temporary effect lasting a median of 22 weeks on average, 11% of patients treated with intraglandular BoNT-A, as reported by Scheffer et al.,<sup>4</sup> noticed an effect beyond 33 weeks and a handful of children experienced continued drooling relief until 1 year after injection.<sup>4</sup> This carry-over effect might have negatively influenced the results of bilateral submandibular duct ligation since the mean time between BoNT-A treatment and baseline bilateral submandibular duct ligation was 9.7 months (SD 5.7). This might have led to a significantly lower drooling quotient baseline value before bilateral submandibular duct ligation and a relatively higher 32-week drooling quotient after bilateral submandibular duct ligation, which was not reflected in the subjective (VAS) impression of caregivers. Another explanation for this phenomenon might be a learning effect. Patients learn to better manage their saliva as they grow older; this might be reinforced by the reduced production of saliva after BoNT-A treatment.

In conclusion, this study suggests that BoNT-A and bilateral submandibular duct ligation are both effective in reducing drooling severity in the short term, whereas bilateral submandibular duct ligation as surgical therapy provides a greater subjective effect at both 8 (short-term) and 32 (medium-term) weeks compared to BoNT-A treatment. Nonetheless, BoNT-A treatment is widely used and treatment success in response to BoNT-A does not predict a

successful response to subsequent bilateral submandibular duct ligation. However, clinical relevance of bilateral submandibular duct ligation among the current modalities used to treat drooling is cautiously suggested by the results of this study. Bilateral submandibular duct ligation should be considered when children or their parents experience inadequate benefits from conservative treatment modalities, when the burden of BoNT-A outweighs its benefits, or when SMDR and bilateral submandibular gland excision surgeries are rejected.<sup>26-31</sup> Bilateral submandibular duct ligation is accompanied by minimal morbidity and offers a potentially definitive solution in contrast to BoNT-A injections. Given the lack of evidence for a long-term effect and particularly in cases of anterior drooling (visible drooling), indication for bilateral submandibular duct ligation should be carefully considered because bilateral submandibular duct ligation

interferes with SMDR, which is currently the most effective therapeutic option to treat drooling in our experience. Yet, SMDR is contraindicated in cases of posterior drooling; therefore, bilateral submandibular duct ligation could be indicated as the first surgical step after BoNT-A treatment. Future studies should focus on bilateral submandibular duct ligation in a larger patient population with a longer follow-up period to further define the long-term effect and externally validate predictors for treatment success or failure,<sup>32</sup> thereby establishing the place of bilateral submandibular duct ligation within the current spectrum of treatment modalities for the treatment of drooling.

## ACKNOWLEDGEMENTS

The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

## REFERENCES

1. 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**: 1032-6.
2. 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.
3. Erasmus CE, van Hulst K, Rotteveel JJ, Willemsen MA, Jongerius PH. Clinical practice: swallowing problems in cerebral palsy. *Eur J Pediatr* 2012; **171**: 409-14.
4. Scheffer AR, 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.
5. 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.
6. van Hulst K, Kouwenberg CV, Jongerius PH, et al. Negative effects of submandibular botulinum neurotoxin A injections on oral motor function in children with drooling due to central nervous system disorders. *Dev Med Child Neurol* 2017; **59**: 531-7.
7. Glynn F, O'Dwyer TP. Does the addition of sublingual gland excision to submandibular duct relocation give better overall results in drooling control? *Clin Otolaryngol* 2007; **32**: 103-7.
8. Mankarious LA, Bottrill ID, Huchzermeyer PM, Bailey CM. Long-term follow-up of submandibular duct rerouting for the treatment of sialorrhea in the pediatric population. *Otolaryngol Head Neck Surg* 1999; **120**: 303-7.
9. Syeda F, Ahsan F, Nunez DA. Quality of life outcome analysis in patients undergoing submandibular duct repositioning surgery for sialorrhoea. *J Laryngol Otol* 2007; **121**: 555-8.
10. De M, Adair R, Golchin K, Cinnamon MJ. Outcomes of submandibular duct relocation: a 15-year experience. *J Laryngol Otol* 2003; **117**: 821-3.
11. Burton MJ, Leighton SE, Lund WS. Long-term results of submandibular duct transposition for drooling. *J Laryngol Otol* 1991; **105**: 101-3.
12. Reed J, Mans CK, Brietzke SE. Surgical management of drooling: a meta-analysis. *Arch Otolaryngol Head Neck Surg* 2009; **135**: 924-31.
13. Delsing CP, Viergever T, Honings J, van den Hoogen FJ. 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.
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.
15. 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.
16. Bekkers S, Delsing CP, Kok SE, et al. Randomized controlled trial comparing botulinum vs surgery for drooling in neurodisabilities. *Neurology* 2019; **92**: e1195-e1204.
17. 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**: 1121-6.
18. Osailan SM, Proctor GB, McGurk M, Paterson KL. Intraoral duct ligation without inclusion of the parasympathetic nerve supply induces rat submandibular gland atrophy. *Int J Exp Patbol* 2006; **87**: 41-8.
19. Shirley WP, Hill JS, Woolley AL, Wiatrak BJ. Success and complications of four-duct ligation for sialorrhoea. *Int J Pediatr Otorhinolaryngol* 2003; **67**: 1-6.
20. Stamataki S, Behar P, Brodsky L. Surgical management of drooling: clinical and caregiver satisfaction outcomes. *Int J Pediatr Otorhinolaryngol* 2008; **72**: 1801-5.
21. Khan WU, Islam A, Fu A, et al. Four-duct ligation for the treatment of sialorrhoea in children. *JAMA Otolaryngol Head Neck Surg* 2016; **142**: 278-83.
22. Martin TJ, Conley SF. Long-term efficacy of intra-oral surgery for sialorrhoea. *Otolaryngol Head Neck Surg* 2007; **137**: 54-8.
23. Scheffer AR, Erasmus C, van Hulst K, et al. Botulinum toxin versus submandibular duct relocation for severe drooling. *Dev Med Child Neurol* 2010; **52**: 1038-42.
24. Gonzalez-L MD, Martinez C, Bori y Fortuny I, Suso-Vergara S. Factors in the efficacy, safety, and impact on quality of life for treatment of drooling with botulinum toxin type A in patients with cerebral palsy. *Am J Phys Med Rehabil* 2017; **96**: 68-76.
25. Schroeder AS, Kling T, Huss K, et al. Botulinum toxin type A and B for the reduction of hypersalivation in children with neurological disorders: a focus on effectiveness and therapy adherence. *Neuropediatrics* 2012; **43**: 27-36.
26. Puraviappan P, Dass DB, Narayanan P. Efficacy of relocation of submandibular duct in cerebral palsy patients with drooling. *Asian J Surg* 2007; **30**: 209-15.
27. Greensmith AL, Johnstone BR, Reid SM, Hazard CJ, Johnson HM, Reddihough DS. Prospective analysis of the outcome of surgical management of drooling in the pediatric population: a 10-year experience. *Plast Reconstr Surg* 2005; **116**: 1233-42.
28. Delsing CP, Cillessen E, Scheffer A, van Hulst K, Erasmus CE, van den Hoogen FJ. Bilateral submandibular gland excision for drooling: our experience in twenty-six children and adolescents. *Clin Otolaryngol* 2015; **40**: 285-90.
29. Berini-Ayres L, Gay-Escoda C. Morbidity associated with removal of the submandibular gland. *J Craniomaxillofac Surg* 1992; **20**: 216-9.
30. Springborg LK, Møller MN. Submandibular gland excision: long-term clinical outcome in 139 patients operated in a single institution. *Eur Arch Otorhinolaryngol* 2013; **270**: 1441-6.
31. Jongerius PH, van Hulst K, van den Hoogen FJA, Rotteveel JJ. The treatment of posterior drooling by botulinum toxin in a child with cerebral palsy. *J Pediatr Gastroenterol Nutr* 2005; **41**: 351-3.
32. 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; <https://doi.org/10.1007/s00415-020-09735-1>. [Epub ahead of print].