ARTICLE CLASS OF EVIDENCE

Randomized controlled trial comparing botulinum vs surgery for drooling in neurodisabilities

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Abstract

Objective

To compare the effect of submandibular duct ligation (2-DL) and submandibular botulinum neurotoxin type A (BoNT-A) for drooling in children and adolescents with neurodevelopmental disabilities.

Methods

A randomized, interventional, controlled, and partly single-blinded study was performed in which submandibular BoNT-A was compared with 2-DL to treat excessive drooling. Main outcomes included a Visual Analog Scale (VAS), drooling quotient (DQ), drooling severity (DS) scale and drooling frequency (DF) scale. Each was obtained at baseline, and 8 and 32 weeks post treatment.

Results

Fifty-seven patients (mean age: 11 years, mean baseline VAS score 7.9, mean baseline DQ 27.3%) were randomized to the 2-DL or BoNT-A group. Four patients were excluded from analyses, leaving 53 patients for intention-to-treat analyses. Response to treatment, defined as a ≥50% reduction in DQ or VAS score, was higher for 2-DL after 32 weeks (63.0% vs 26.9%, $p = 0.008$). Both VAS score (24.5, $p < 0.001$) and DQ (−9.3%, $p = 0.022$) were significantly lower at follow-up after 2-DL vs BoNT-A. The total number of adverse events ($p = 0.088$, 40.7% vs 19.2%) and postoperative complaints was higher ($p < 0.001$, mean 9.6 vs 3.6 days) for 2-DL than for BoNT-A.

Conclusion

The 2-DL procedure is a more effective treatment for drooling than botulinum toxin, but carries a slightly greater risk of complications and morbidity.

Trialregister.nl identifier

NTR3537.

Classification of evidence

This study provides Class III evidence that for children and adolescents with neurodevelopmental disabilities and severe drooling, 2-DL compared to a one-time intraglandular BoNT-A injection is more effective at reducing drooling at 32 weeks.

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Glossary

AE = adverse event; **BoNT-A** = botulinum neurotoxin type A; **CI** = confidence interval; **CP** = cerebral palsy; **DF** = drooling frequency; **2-DL** = 2-duct ligation (bilateral submandibular duct ligation); **DQ** = drooling quotient; **DS** = drooling severity; **NNT** = number needed to treat; **SAE** = serious adverse event; **SMDR** = submandibular duct relocation; **SMGE** = submandibular gland excision; **VAS** = Visual Analog Scale.

Drooling is a common problem in children with cerebral palsy (CP) and other neurodevelopmental disabilities as approximately 40% of the children with CP experience drooling.[1] Drooling is a disabling condition associated with physical and emotional distress.[2–4]

Current treatment and its limitations

If drooling proves refractory to conservative treatment (speech or behavioral therapy), or patients are ineligible for conservative or systemic treatment, intraglandular botulinum neurotoxin type A (BoNT-A) can be considered.[5] Injected under general anesthesia, it is effective in approximately 50% of children for a median of 22 weeks.[3] Botulinum toxin by nature has only a limited duration of effect. If drooling persists despite repeated injections, patients and caregivers often express a desire for a more permanent solution. Surgical techniques such as submandibular gland excision (SMGE) and submandibular duct relocation (SMDR) are effective in a majority of patients.[6–10] Both have several downsides, however: SMGE is associated with external scars, while SMDR is a more technically challenging procedure and is contraindicated in posterior drooling.[11–13] Both procedures are also associated with significant operative time, and in the case of SMDR, requires several days hospitalization. Submandibular duct ligation (2-DL) recently gained popularity as a minimally invasive, simple, and short procedure with limited dissection and perioperative morbidity that appears to rival BoNT injections.[14] However, the effectiveness of 2-DL is less well established than SMDR and SMGE. This randomized clinical trial compares the effect of 2-DL to BoNT-A for drooling in children and adolescents with neurodevelopmental disabilities.

Methods

Trial design

The study was designed as a randomized controlled trial. In the early stage of the study, one inclusion criterion was changed because of insufficient inclusion: the requirement for previous treatment with BoNT-A prior to inclusion was dropped. Also, the minimum age of inclusion was increased from 6 to 8 years to give each child maximum opportunity to develop. Both changes were approved by the regional ethics committee. The study was partially blinded: 8- and 32-week follow-up drooling quotient (DQ) measurements were recorded on video. A separate speech language therapist blinded to therapy allocation measured the DQ using these video recordings.

Study design

This interventional, randomized, controlled trial for drooling in children and adolescents with neurodevelopmental disabilities, was conducted in Nijmegen, the Netherlands between April 2012 and August 2017.

Standard protocol approvals, registrations, and patient consents

This study was performed following approval from an independent regional ethics committee and was registered in the Dutch Trial Register (trialregister.nl identifier: NTR3537). Written informed consent was obtained from all guardians of the participants in the study.

Participants

Patients were seen at the regular outpatient Saliva Control clinic of the Radboud University Medical Centre and were assessed for eligibility by our Saliva Control team including a pediatric neurologist, a pediatric speech-language therapist, a rehabilitation specialist, and an ear, nose, and throat surgeon. Children who reported severe drooling, whose conservative treatment had failed or was not expected to provide adequate relief, were eligible for inclusion. All patients who were cognitively capable underwent oral therapy to maximize mouth closure. Patients were enrolled by the study coordinator. To prevent a carryover effect, interventions only took place 6 months after the last previous treatment. Inclusion criteria were as follows:

1. Severe drooling (drooling frequency [DF] scale score ≥3 or drooling severity [DS] scale score ≥2)[15]
2. Aged 8 years and older
3. CP or any other nonprogressive neurodevelopmental disability
4. Ability and willingness to follow the study protocol and attend the 8- and 32-week visits
5. Written and informed consent from caregivers, and when appropriate, oral consent from the child

Patients with potentially progressive oromotor impairment, those who were receiving medical treatment (glycopyrrolate or scopolamine) at the time of inclusion, those with a surgical history intervening with 2-DL, those with any other contraindication for general anesthesia, BoNT-A injections, or surgery, or those who used benzodiazepines, were excluded from the study. Concurrent use of benzodiazepines was part of the exclusion criteria because of potential influences on the

swallowing process, thus causing increased drooling, particularly at high doses.[16]

Interventions

After baseline assessment, patients were randomized to BoNT-A or 2-DL. Onabotulinum toxin A (25 U in 0.9% saline per submandibular salivary gland; Botox; Allergan, Nieuwegein, the Netherlands) was administered under general anesthesia in a single procedure using ultrasonographic guidance with a 25-gauge needle and a 1-mL syringe.[17] Only the submandibular glands were injected. In our institution, combined BoNT-A injections in both the submandibular and the parotid glands are generally only considered if there has been insufficient response to submandibular injections.[18] The 2-DL procedure was also performed under general anesthesia. The floor of the mouth was infiltrated with 1% lidocaine with 1:100.000 epinephrine, and incised parallel to the frenulum. After identification of the duct, it was dissected for 1 to 2 cm and ligated using a disposable stapler, applying 2 vascular clips per duct. The incision was closed with absorbable sutures.

Both procedures were performed in an outpatient setting, and all patients allocated to 2-DL received antibiotics (amoxicillin/clavulanic acid) for 7 days and analgesics (paracetamol and diclofenac) for 5 days postoperatively.

Randomization

Patients were randomly assigned by the research associates in a 1:1 ratio using a centrally held, statistician primed, computer-generated randomization sequence stratified by CP or other neurodevelopmental disability, Gross Motor Function Classification System, and sex allowing concealment for the next allocation. In case of withdrawal before the intervention had taken place, new patients were included.

Masking

The study was partially blinded: 8- and 32-week follow-up DQ measurements were recorded on video. A separate speech language therapist blinded to therapy allocation measured the DQ using these video recordings, which allowed us to determine interrater accuracy and check for researcher bias. Thus, only investigators who measured the DQ recorded on video were blinded. Patients, caregivers, and investigators were not otherwise masked for treatment allocation.

Visits

The follow-up protocol closely matches regular care in our Saliva Control clinic. Visits were performed at baseline and 8 and 32 weeks postoperatively for evaluation of the primary and secondary outcome measures. One week after the intervention, caregivers were contacted by telephone and asked about complaints and adverse events (AEs). Caregivers completed a diary assessing complaints postoperatively.

Primary outcome measures

Measurements were made by experienced pediatric speech-language therapists. The primary outcome was the comparison of 2-DL to BoNT-A for response to treatment at 32 weeks, defined as ≥50% reduction in the DQ or caregiver's Visual Analog Scale (VAS) score.

The DQ, a validated, direct observational, semiquantitative method to assess severity of drooling, reflects the proportion of new saliva dripping over the lips over a 5-minute session as observed during activity or rest.[17] In this study, we report the DQ in activity.[19] To increase reliability, measurements take place at least 1 hour after a meal while awake and sitting erect.

The VAS is marked on a 100-mm line and reflects severity of drooling over the previous 2 weeks. A score of 100 corresponds to severe drooling.

This study provides Class III evidence that for children and adolescents with neurodevelopmental disabilities and severe drooling, 2-DL compared to a one-time intraglandular submandibular BoNT-A injection is more effective at reducing drooling at 32 weeks.

Secondary outcome measures

1. Changes in VAS score following 2-DL and BoNT-A
2. Changes in DQ following 2-DL and BoNT-A
3. Response to treatment 8 weeks after treatment
4. Changes in DS and DF scale scores after 8 and 32 weeks
5. Procedural time
6. Complaints as reported by caregivers in a diary over the first 2 weeks postoperatively
7. AEs were graded as related or unrelated to the intervention, and AEs or serious AEs (SAEs) when potentially life-threatening, requiring prolonged hospitalization, or causing permanent damage.[20] Pain, dysphagia, xerostomia for less than 7 days were considered normal postoperative course.

Statistical analysis

The sample size was estimated based on outcomes in previous studies. Forty percent response to BoNT-A and 80% response to 2-DL indicates that 26 patients per arm would provide 80% power to detect a difference with a type I error rate of 5% including a 10% dropout rate.

Analyses were by intention to treat unless otherwise stated. Data analysis included descriptive statistics to summarize demographics; Pearson χ^2 statistics to treatment response; mixed-model analyses with random intercepts was performed to test whether change in VAS and DQ differ between interventions; unpaired samples t test to procedural time, total days of complaints, and number of AEs and Wilcoxon rank test to change in DS/DF in subsequent visits. We report p values, and differences (absolute risk reduction) and numbers needed to treat (NNT) bounded by confidence intervals (CIs) when applicable.

Data availability

The protocol and anonymized demographics and data regarding the primary and secondary study outcomes will be shared by request from any qualified investigator.

Results

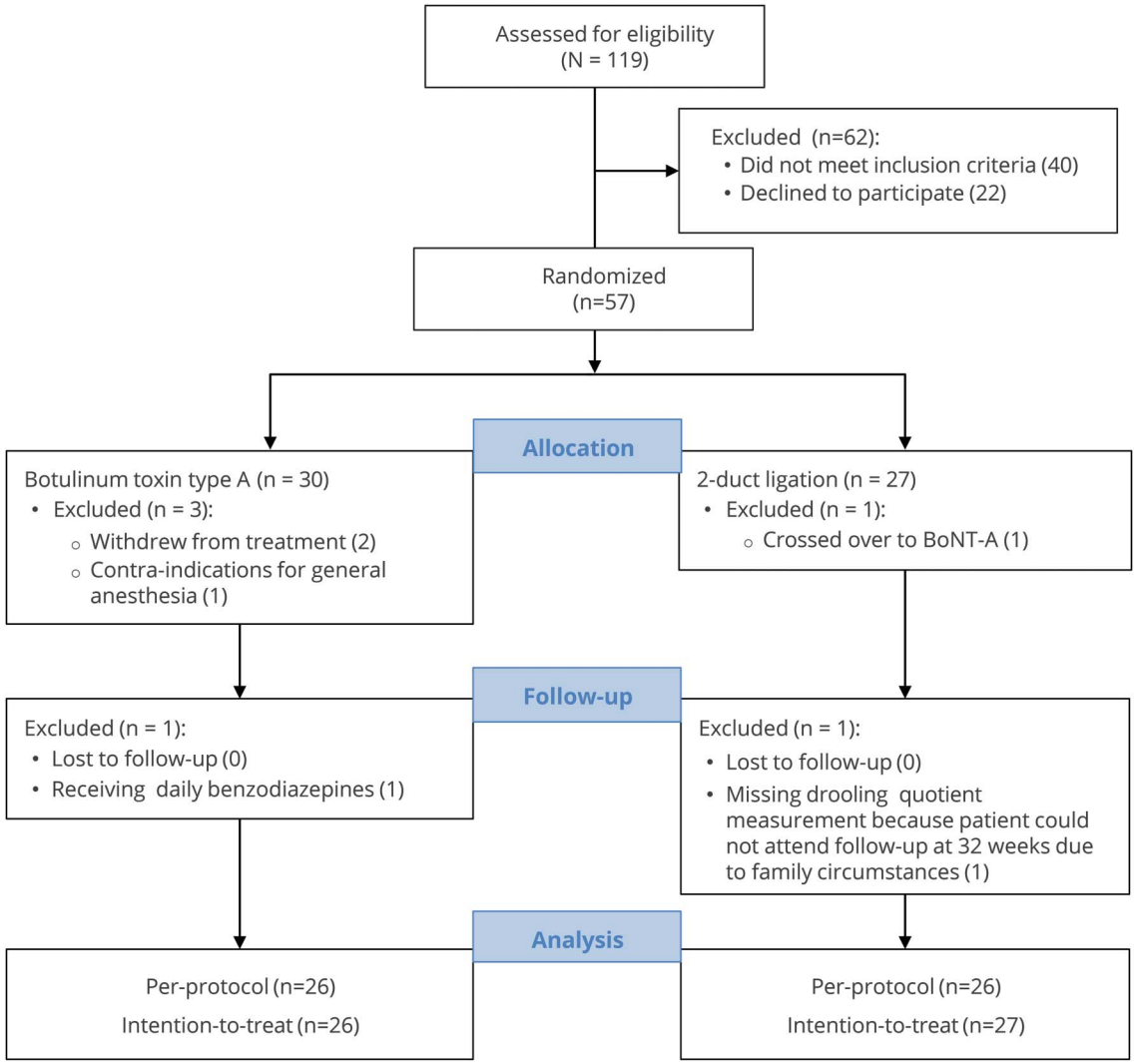
We screened 119 children for eligibility. Forty children did not meet inclusion criteria. Twenty-two children or caregivers were not willing to participate. Fifty-seven patients were thus randomized for treatment allocation (figure 1).

Demographics were closely matched (table 1) and there were no significant differences between the treatment arms at baseline. Four children were previously treated with anticholinergic medication prescribed by clinicians in other (some of them foreign) institutions. Among these 4 patients, 3 children were treated with glycopyrrolate and one patient was treated with scopolamine patches. Reasons for discontinuation and referral were lack of effect and side effects. Follow-up attendance at 8 weeks was 100% and 98.1% at 32 weeks. Missing data were limited: the DQ was missing for 2 patients at 8 weeks and for 4 patients at 32 weeks. One patient was not able to attend for 32 weeks visit because of personal circumstances. For this patient, the subjective measurements were obtained by telephone. For 2 patients, the DQ at 8 and 32 weeks was unreliable due to spitting of saliva during the assessment. For one patient, the DQ at 32 weeks was omitted because the patient kept her hands in her mouth during the measurement. For another patient, the "DQ during activity" at 32 weeks was substituted with "DQ in rest" because of unreliable measurements of DQ during activity. There were 10 (18.9%) and 16 (30.2%) missing values for the masked DQ at 8 weeks and 32 weeks, respectively.

Primary outcome

Sixty-three percent of children showed a clinically significant response (≥50% reduction in the DQ or caregiver's VAS score) to 2-DL after 32 weeks, vs 26.9% for BoNT-A (difference 36.1%, 95% CI 18.1–54.1, NNT 3, 95% CI 2–6). After 8 weeks, this was 88.9% for 2-DL and 53.8% for BoNT-A

Figure 1 Flow diagram of recruited patients



BoNT-A = botulinum neurotoxin type A.

Table 1 Baseline demographic and clinical characteristics (intention-to-treat population)

	BoNT-A (n = 26)	2-DL (n = 27)
Age, y, mean ± SD	11.2 ± 2.5	11.1 ± 3.2
Sex, female, n (%)	11 (42.3)	11 (40.7)
Main diagnosis, n (%)		
Spastic CP	10 (38.5)	6 (22.2)
Dyskinetic CP	1 (3.8)	3 (11.1)
Spastic/dyskinetic CP	5 (19.2)	5 (18.5)
CP, type is missing	1 (3.8)	0
Other developmental disability	9 (34.6)	13 (48.1)
GMFCS level,[a] score only applies to CP (n = 31), n (%)		
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
Degree of disability, applies to all participants n (%)		
Ambulant	11 (42.3)	10 (37.0)
Nonambulant	15 (57.7)	17 (63.0)
Developmental age, n (%)		
<4 y	15 (57.7)	15 (55.6)
>4 y	11 (42.3)	12 (44.4)
Epilepsy, n (%)		
Yes	17 (65.4)	15 (55.6)
Controlled	13 (76.5)	13 (86.7)
Intractable	4 (23.5)	2 (13.3)
No	9 (34.6)	12 (44.4)
GERD, n (%)		
Yes	8 (30.8)	9 (33.3)
No	18 (69.2)	18 (66.7)
Dental malocclusion, n (%)		
Normal occlusion	9 (36.0)	7 (26.9)
Mild malocclusion	8 (32.0)	13 (50.0)
Severe malocclusion	8 (32.0)	6 (23.1)
Missing	1	1
Mouth closure, n (%)		
Normal mouth closure	1 (3.8)	0
Incomplete mouth closure	9 (34.6)	7 (26.9)
Mouth constantly open	16 (61.5)	19 (73.1)
Missing	0	1
Gastrostomy feeding, n (%)		
Oral	16 (61.5)	20 (74.1)
Gastrostomy/gastrostomy and oral (no pharyngeal swallowing problem)	10 (38.5)	7 (25.9)
BoNT-A pretrial		
Yes, n (%)	15 (57.7)	17 (63.0)
No, n (%)	11 (42.3)	10 (37.0)
Mean BoNT-A, n ± SD	1.6 ± 1.8	1.4 ± 1.3

Abbreviations: BoNT-A = botulinum neurotoxin type A; CP = cerebral palsy; 2-DL = 2-duct ligation; GERD = gastroesophageal reflux disease; GMFCS = Gross Motor Function Classification System.
[a] GMFCS I–III are classified as ambulant; GMFCS IV and V are classified as nonambulant.

(difference 35.1%, 95% CI 23.6–46.6, NNT 3, 95% CI 2–4). When substituting the DQ with the (video-evaluated) masked DQ at 32 weeks, the response to 2-DL was 72.0% vs 26.9% to BoNT-A (difference 45.1%, 95% CI 32.9–57.4, NNT 2, 95% CI 2–3). After 8 weeks, this was 92.6% vs 57.7%, respectively (difference 34.9, 95% CI 24.0–45.8, NNT 3, 95% CI 2–4). There was a significant association between VAS and DQ at baseline ($r = 0.29$, $p = 0.039$), 8 weeks ($r = 0.52$, $p < 0.001$), and 32 weeks ($r = 0.39$, $p = 0.006$).

VAS for severity of drooling

The VAS at follow-up was significantly lower after 2-DL when compared to BoNT-A (figure 2, table 2) using mixed-model analyses. For both BoNT-A and 2-DL, VAS was significantly (difference 19.4, $p < 0.001$, 95% CI 10.2–28.5) higher at 32 weeks when compared to 8 weeks. This increase did not significantly differ between the 2 interventions.

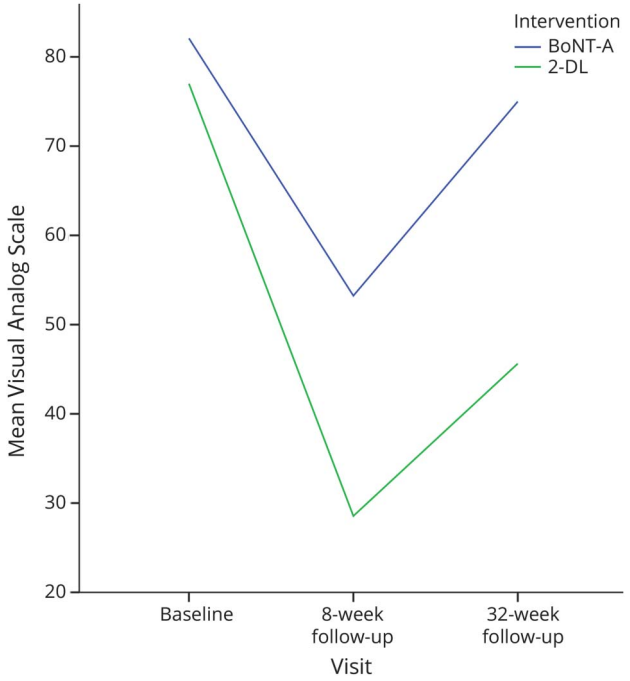
Drooling quotient

The DQ at follow-up was 9.3% lower after 2-DL when compared to BoNT-A (figure 3, table 2). For both interventions, the DQ was significantly (difference 7.3%, $p = 0.007$, 95% CI 2.1%–12.5%) higher at the 32-week interval than after the 8-week interval. This increase did not significantly differ between the 2 interventions. There was a strong correlation between the regular, unblinded DQ, and the "blinded DQ" that was based on video recordings. Furthermore, outcomes and significance for the mixed-model analyses and response to treatment analyses when imputing "masked DQ" instead of unmasked DQ were similar.

DS and DF

BoNT-A did not lead to a significant reduction in DS after 8 or 32 weeks. The 2-DL did lead to a significant decrease in DS

Figure 2 Visual Analog Scale



BoNT-A = botulinum neurotoxin type A; 2-DL = 2-duct ligation.

after 8 weeks (table 2), but this did not persist after 32 weeks. There was a significant reduction in DF both 8 and 32 weeks after BoNT-A. This reduction was greater after 2-DL.

Procedural time

Per-protocol analysis showed that, on average, BoNT-A was a significantly shorter procedure than 2-DL (6:13 vs 21:23 minutes).

Adverse events

There were more AEs after 2-DL than after BoNT-A (40.7% vs 19.2%, difference 21.5%, CI −11.2% to 54.2%) (table 3). There were 3 cases of SAEs, which included 3 admissions: one patient due to nausea postoperatively, which was related to the intervention, one patient due to nausea unrelated to the intervention, and one patient for dehydration due to gastroenteritis, which was unrelated to the intervention. All other complications were related to the intervention except for one patient with pharyngitis. There was no long-lasting disability as all AEs had resolved within 6 weeks and there were no cases of wound infection, postoperative bleeding, or ranula formation warranting surgical reintervention.

Complaints

Thirty-nine of 53 patients completed the postoperative complaints diary (table 3). The total number of days of complaints was significantly lower (difference 6.5 days, 95% CI 4.0–8.9) after BoNT-A (mean 3.1 ± 3.6 days) than after 2-DL (mean 9.6 ± 3.9 days).

Discussion

The purpose of this randomized controlled trial was to compare the effect of 2-DL with BoNT-A for drooling in neurodevelopmentally disabled children and adolescents. Response to treatment, defined as a 50% reduction in (the objective outcome) DQ or (the subjective outcome) VAS, was significantly higher at both 8 and 32 weeks after 2-DL compared to BoNT-A. Response for both interventions declined after 32 weeks compared to 8 weeks postintervention.

This decline in response was expected for BoNT-A, since it is by nature a short-term agent. However, there was an unexpected similar decline in response 32 weeks after 2-DL, which is in contrast with an animal study that reported atrophy in histologic examination, and loss of function of the acinar cells after unilateral submandibular 2-DL.[12,21] The decline in response after 2-DL is also unlike our experience with SMGE, where we saw a greater effect in both objective and subjective outcomes 32 weeks postoperatively.[6] We cannot fully explain the difference in effect between SMGE and 2-DL; perhaps the formation of alternative salivary pathways contributes to renewed drooling after 2-DL.[11,14]

Recurrence of drooling in the medium term after 2-DL has been reported in previous studies. We found that 25.9% of the present population stopped responding in the period between 8 and 32 weeks' follow-up, whereas recent studies reported 0% recurrence in 15 patients with 8 months' follow-up,[14] and 7 of 12 patients (58%) after a mean of 16 months' follow-up using ligatures.[11] This variation can perhaps be explained by a greater length of follow-up or the use of ligatures rather than vascular clips in the latter study. We think ligatures might carry an increased risk of slippage and increased tissue traction reaction, which would ultimately lead to alternative salivary pathway formation and thereby recurrence of drooling.[13] Future studies should focus on the reason of recurrence, and what could be done to prevent it.

Although the DS did not diminish significantly following treatment, the DF was significantly reduced. One possible explanation for this difference is that the submandibular gland is responsible for two-thirds of the total saliva in the unstimulated situation where the parotid gland is accountable for the majority of the total saliva in the stimulated situation.[22] The result of treatment to the submandibular glands is mainly a relative reduction of the salivary flow in rest, which leads to less frequent drooling throughout the day. However, the untreated parotid gland is the major source of saliva in stimulated situations. In these situations, it is therefore logical that the severity of drooling remains the same. Combined BoNT-A injections to both the submandibular and parotid glands could possibly match the effect of 2-DL, and internationally it is common to treat both the submandibular and the parotid gland at one time initially. In our institution, combined injections are only considered when there was no or insufficient response of submandibular botulinum toxin

Table 2 Outcomes (intention-to-treat population)

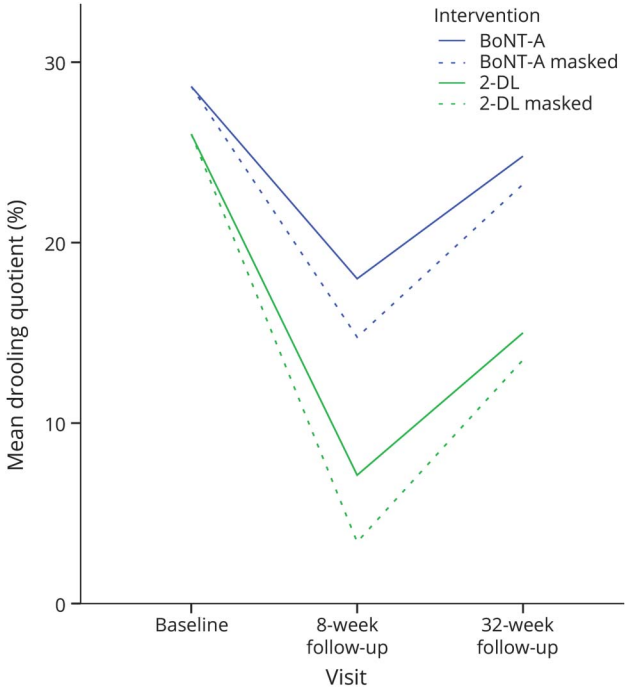
	BoNT-A, mean ± SD	2-DL, %, mean ± SD	Change	
			B (95% CI)	*p*
DQ, %				
Baseline	28.7 ± 23.9	26.0 ± 21.8	—	
8 wk	18.0 ± 19.6	7.1 ± 10.0	9.3 (1.4–17.2)	0.022
32 wk	24.8 ± 25.0	15.0 ± 17.4		
VAS[a]				
Baseline	82.1 ± 16.2	77.0 ± 15.7	—	
8 wk	53.2 ± 32.3	28.6 ± 24.2	24.5 (13.2–35.7)	<0.001
32 wk	75.0 ± 23.0	45.6 ± 28.3		

DS	BoNT-A, n (%)					Change		2-DL, n (%)					Change	
						z	*p*						*z*	*p*
	1, Dry	2, Mild	3, Moderate	4, Severe	5, Profuse			1, Dry	2, Mild	3, Moderate	4, Severe	5, Profuse		
Baseline	—	—	4 (15)	3 (12)	19 (73)	—		—	—	2 (7)	8 (30)	17 (63)	—	
8 wk	—	1 (4)	3 (12)	8 (31)	14 (54)	−1.3	0.207	1 (4)	3 (11)	11 (41)	5 (18)	7 (26)	−3.7	<0.001
32 wk	—	1 (4)	1 (4)	6 (23)	18 (69)	0	1.0	—	3 (11)	3 (11)	7 (26)	14 (52)	−1.9	0.061

DF	BoNT-A, n (%)				Change		2-DL, n (%)				Change	
					z	*p*					*z*	*p*
	1, Never	2, Occasional	3, Frequent	4, Constant			1, Never	2, Occasional	3, Frequent	4, Constant		
Baseline	—	1 (4)	9 (35)	16 (62)	—		—	2 (7)	11 (41)	14 (52)	—	
8 wk	—	10 (38)	9 (35)	7 (27)	−3.2	0.001	2 (7)	18 (67)	6 (22)	1 (4)	−4.2	<0.001
32 wk	—	5 (19)	11 (42)	10 (38)	−2.4	0.019	—	15 (56)	7 (26)	5 (19)	−3.3	0.001

Abbreviations: BoNT-A = botulinum neurotoxin type A; CI = confidence interval; DF = drooling frequency; 2-DL = 2-duct ligation; DQ = drooling quotient; DS = drooling severity; VAS = Visual Analog Scale.
[a] VAS = caregivers scale for severity of drooling over the past 2 weeks.

Figure 3 Drooling quotient



BoNT-A = botulinum neurotoxin type A; 2-DL = 2-duct ligation.

Table 3 AEs and complaints

	BoNT-A (n = 26)	2-DL (n = 27)	*p* Value
Total n (%) of AEs	5 (19.2)	11 (40.7)	0.088
AEs, n (%)	5 (19.2)	8 (29.6)	
Dysphagia	2 (7.7)	1 (3.7)	
Xerostomia		2 (7.4)	
Prolonged pain medication		3 (11.1)	
Diminished feeding due to nausea	1 (3.8)		
Antibiotics for pneumonia, n (%) possibly related to the intervention	1 (3.8)	2 (7.4)	
Antibiotics for pharyngitis	1 (3.8)[a]		
SAEs, n (%)	0	3 (11.1)	
Admission due to nausea, n (%) related to the intervention		1 (3.7)	
Admission due to nausea, n (%) unrelated to the intervention		1 (3.7)[a]	
Admission because of dehydration due to gastroenteritis		1 (3.7)[a]	
Completed the complaints diary, n	18	21	
Mean days of complaints ± SD	3.1 ± 3.6	9.6 ± 3.9	<0.001
Mean days of pain ± SD	0.3 ± 0.5	4.1 ± 4.1	
Mean days of diminished feeding ± SD	1.4 ± 2.0	5.1 ± 4.4	
Mean days of swelling of the submandibular region ± SD	0.4 ± 1.1	5.8 ± 5.2	
Mean days of tiredness, irritability, or apathy ± SD	1.7 ± 2.4	6.1 ± 4.5	

Abbreviations: AE = adverse event; BoNT-A = botulinum neurotoxin type A; 2-DL = 2-duct ligation; SAE = serious adverse event.
[a] Unrelated to the intervention.

injections because we find that some degree of patients are overtreated when initially combining injections, and to limit morbidity.[18]

We compared the effectiveness, morbidity, patient's satisfaction, and procedural time of BoNT-A and 2-DL in a prospectively controlled setting. In contrast with prior literature, there were no complications of 2-DL requiring surgical reintervention.[14] Complaints after 2-DL were all temporary, and patients were free of complaints after a mean of 10 days. Even though there were 3 SAEs after 2-DL, there seemed to be no direct relation between the intervention and 2 SAEs. Procedural time and thereby time under general anesthesia for BoNT-A injections was significantly shorter, and BoNT-A was associated with fewer postoperative complaints than 2-DL, and there were fewer complications (19.2% vs 40.7%) after BoNT-A. Prior studies reported 0% to 33% AEs after BoNT-A injections, which is analogous to the proportion of AEs in this study.[5,23,24] In conclusion, the morbidity of BoNT-A is less than for 2-DL. However, it could be argued that this is to some extent offset by the fact that BoNT-A injections will usually have to be repeated to maintain treatment effect.

There is a contrast in reported response to treatment at 8 and 32 weeks after BoNT-A between our study and previous literature regarding effects of submandibular BoNT-A, even those conducted in our own center. The difference is presumably attributable to varying definitions for response to treatment. We found 63.0% and 26.9% response rates after 8 and 32 weeks, respectively, defining response to treatment as a >50% reduction in VAS or DQ. A previous study reported 47% and 15% after 8 and 32 weeks, respectively. "Success" in this study had a more limited definition, however: only a 50% reduction in DQ was considered therapeutic success.[3] Another recent study reported 65% response to treatment 8 weeks after submandibular BoNT-A; response to treatment in this particular study was defined as a 50% reduction in DQ or >2 SDs in VAS.[23] The changing definitions reflect increasing clinical insight, and we think the present definition most closely reflects actual clinical "success." If we would have applied similar "success criteria" as previous studies, the response rate in this study would be 58%.

There are some limitations to this study. First, we changed inclusion criteria to reduce inclusion delay, potentially resulting in an increase in heterogeneity of the patient population. We did not find any evidence to support such an increase in the data, however.

Another potential limitation is the fact that patients, caregivers, and researchers were not blinded to treatment allocation. It should be noted, however, that the masked DQ was closely related to the unmasked DQ, suggesting limited bias. The length of follow-up is another limitation of the study; first, because recurrence seemed ongoing up to 32 weeks after 2-DL. This means that the effectiveness of 2-DL in the long term cannot be fully extrapolated from the current data. Second, the follow-up period is too short to assess potential dental disadvantages from diminished salivary flow.

Since BoNT-A is a short and effective procedure for the treatment of drooling with very few postoperative complaints, BoNT-A injection is considered first-step treatment when conservative treatment measures have failed. However, over time, patients and caregivers frequently prefer a longer-lasting therapy. Thus far, there are no studies proving botulinum toxin mediated glandular atrophy resulting in long-term effect of botulinum toxin.[17,25] Moreover, the effectiveness of repeated BoNT-A injections might be limited as a result of antibody formation, which has been reported in up to 15% of patients.[26–29]

This study suggests that 2-DL can be an effective "follow-up therapy" to BoNT-A: it is more effective and longer lasting, and carries only a slightly greater risk for AEs and complaints. The 2-DL also has specific advantages over SMDR or SMGE: unlike SMDR, it is a viable option in posterior drooling, and unlike SMGE, there is no external scar. It is also a much more limited and shorter procedure than SMDR or SMGE.

If drooling recurs after 2-DL, it is our opinion that either SMGE or parotid duct ligation (either unilateral or bilateral) should be considered. It should be noted that 2-DL precludes subsequent SMDR. This is a significant disadvantage as SMDR is currently one of the most effective surgical treatment options for anterior drooling, and thus should be borne in mind when indicating 2-DL.[30]

We report a randomized controlled trial comparing 2-DL with BoNT-A injections. BoNT-A is an effective treatment for drooling in neurodevelopmentally disabled children with minor risk of AEs and morbidity. The 2-DL is a more effective treatment for drooling that is equally performed in day care, but includes a slightly greater risk of complications and morbidity compared to BoNT-A. The 2-DL should therefore be considered in case of unsatisfactory results after BoNT-A, but only when the child is older than 8 years or when there is a low expectation of "outgrowing" the drooling, and when SMDR is contraindicated or rejected by caregivers considering the irreversible contraindication for SMDR after 2-DL. Future research should focus on predictors for response to treatment, cost-effectiveness, quality of life, and the long-term effect of 2-DL to determine the exact position of 2-DL in treatment of drooling.

Author contributions

S. Bekkers: drafting/revising the study manuscript, data analysis and interpretation of data, biostatistical analyses, preparation of figures and tables, study investigator. C. Delsing: data collection, drafting/revising the study manuscript, study investigator. S. Kok: study design, data collection, drafting/revising the study manuscript, study investigator. K. van Hulst: data collection, drafting/revising the study manuscript. C. Erasmus: data collection, drafting/revising the study manuscript. A. Scheffer: study design, drafting/revising the study manuscript. F. van den Hoogen: study design, drafting/revising the study manuscript, interpretation of data, drafting/revising the study manuscript. All authors have drafted the manuscript for intellectual content and approve the final version to be published.

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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Randomized controlled trial comparing botulinum vs surgery for drooling in neurodisabilities

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