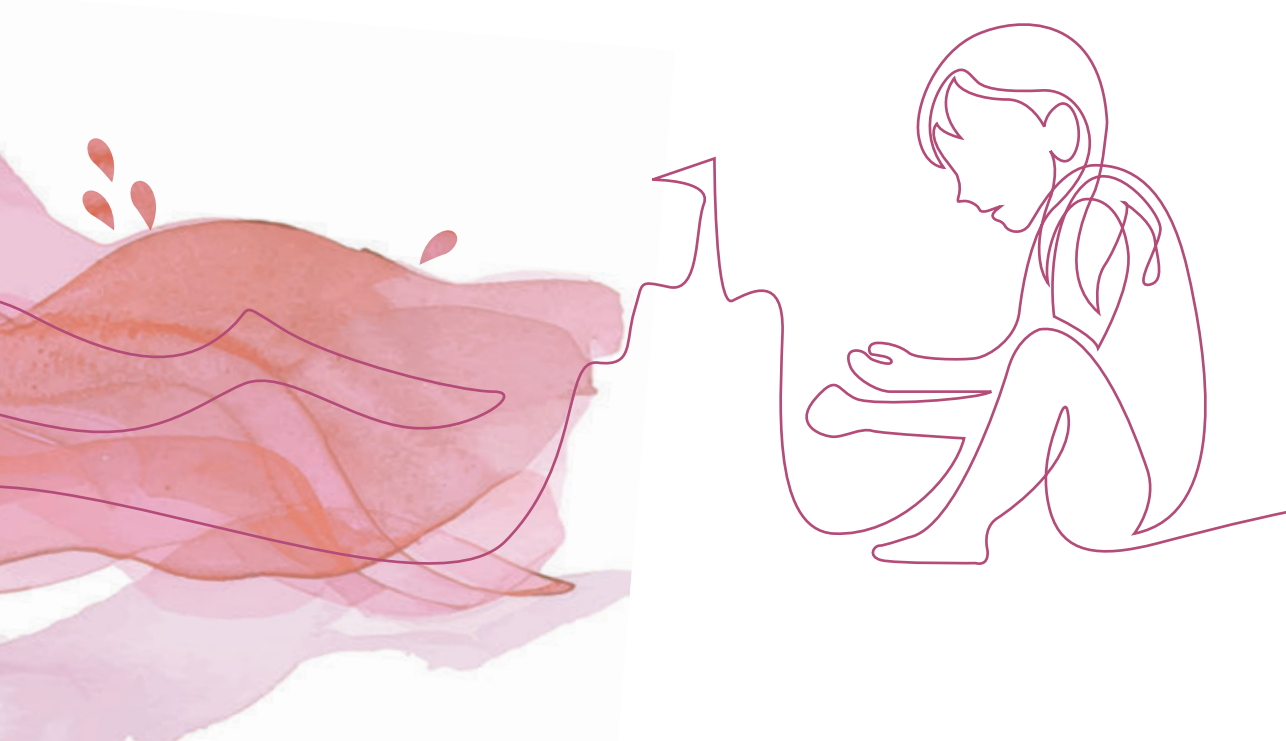
Surgery on the submandibular salivary gland for anterior and posterior drooling in children and adolescents with neurodevelopmental disorders

Corinne Delsing



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Corinne Petronella Antoinette Delsing

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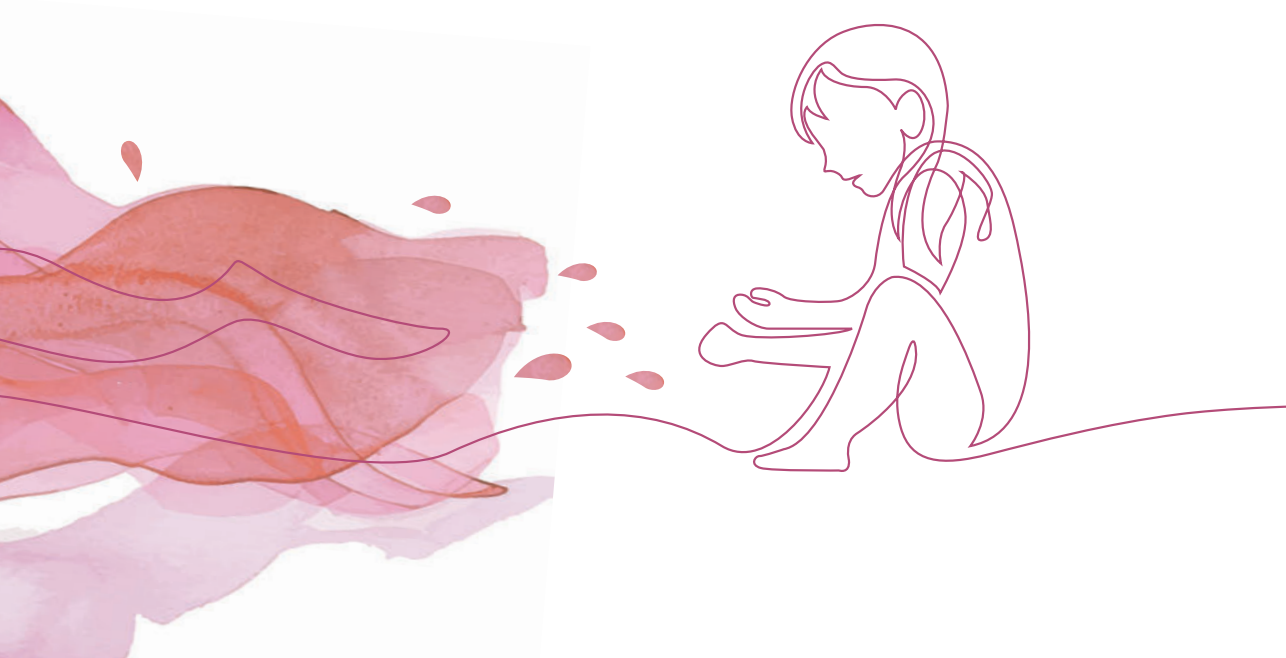
GENERAL INTRODUCTION



About Drooling

Lack of saliva control or drooling is generally considered abnormal after the age of 4 years; nevertheless, a substantial part (3-15%) of preschoolers are still drooling to a certain extent, speculating that drooling in a small group of children older than four years is within the range of normal. [1] [2] In children with neurodevelopmental disabilities, drooling can persist after the age of 4 years due to a swallowing disorder in the oral and/or oropharyngeal phase.

From a clinical point of view, we distinguish between 'anterior' and 'posterior' drooling. [3] Anterior drooling is defined as saliva loss anteriorly from the mouth with visible spilling into the lip area and chin. Anterior drooling is the consequence of diminished oromotor control often in combination with perpetuating factors like abnormal neurological maturation, a poor sitting alignment, or an intellectual disability. Drooling has a wide variety of consequences for the patient and their caregivers. Children suffer from psychosocial and physical complications, including impaired self-esteem, damage to clothing and other materials, an increased burden for caregivers, poor dentition, and perioral infections. [4] In children with neurodevelopmental disabilities, the prevalence of anterior drooling is up to 78%, with a mean prevalence of 44%. [5-8]

Posterior drooling is the spill of saliva over the tongue from the oropharynx into the hypopharynx, with an impaired initiation of the involuntary swallowing reflex. In children with severe oropharyngeal dysphagia, this can lead to the pooling of saliva, leading to congested breathing, gagging, coughing, and saliva aspiration and recurrent or chronic lower respiratory tract infections (LRTIs). [9] Despite aspiration of pathogenic bacteria transmitted by saliva, two more clinical manifestations of chronic pulmonary aspiration have been described: aspiration of toxic contents (i.e., gastric acid); and aspiration of substances (i.e., food). [10]

Chronic aspiration of saliva is challenging to diagnose and, in the long-term, often leads to bronchiectasis, a well-known sequela of chronic aspiration that leads to significant morbidity. [11] To state, LRTIs are described as the most common cause of death in children with cerebral palsy (CP). [12]

The prevalence of posterior drooling is unknown but estimated to be 10-15% in the population with severe neurodevelopmental disabilities.

About salivary glands

Saliva is produced by the salivary glands. The paired parotid, submandibular, and sublingual glands are the major salivary glands. The paired submandibular glands are responsible for the most significant saliva production in rest (65-70%). Secondary, the paired parotid glands are active during gustatory or tactile stimulation and at rest responsible for about 20% of all saliva. When stimulated, this increases. [13] Altogether, humans produce approximately 1-1.5 liters of saliva each day. [14]

The submandibular gland is the second largest of the three main salivary glands. It is located in the submandibular triangle, formed by the body of the mandible, and the anterior, and posterior belly of the digastric muscle. The gland is surrounded by a superficial layer of the deep cervical fascia. It has a superficial and deep lobe separated by the mylohyoid muscle. [15] Saliva is delivered from the submandibular gland through the Wharton's duct, the primary excretory duct, into the oral cavity at the sublingual caruncle. The duct is approximately 5 cm in length and 1.5 mm in diameter. The duct originates at the submandibular gland hilium and travels around the posterior portion of the mylohyoid muscle to cross medially with the lingual nerve towards the sublingual caruncle in the oral cavity. The sublingual caruncle is located medial to the sublingual gland and lateral to each side of the frenulum linguae. Blood supply to the submandibular gland is received from the submental and sublingual arteries, the facial and lingual artery branches, respectively. Both are branches of the external carotid artery. The facial and sublingual veins drain the gland and flow into the internal jugular vein.

The submandibular gland receives sympathetic and parasympathetic innervation. The chorda tympani, a branch of the facial nerve, delivers the parasympathetic input via the submandibular ganglion. The nerve, as a result of this, stimulates secretomotor capacity. The chorda tympani carry the submandibular ganglia's pre-ganglionic fibers. The post-ganglionic fibers reach the submandibular gland and release acetylcholine along with other neurotransmitters, such as substance P and neuropeptide Y. Acetylcholine, the primary neurotransmitter, and the muscarinic receptors, work to stimulate myoepithelial cell function and salivary secretion. Sympathetic nerve cell bodies are located in the superior cervical ganglion and extend post-ganglionic fibers that travel with branches of the external carotid artery to innervate the submandibular gland. Sympathetic input also increases salivary secretion and can induce local inflammation.
The sublingual gland is closely associated with the submandibular gland. The sublingual gland is positioned anterior to the submandibular gland, just below the mucosa of the floor of the mouth. The sublingual gland drains into the small ducts of Rivinus. A larger duct of Bartholin may join Wharton's duct to drain into the sublingual caruncle.

The parotid gland are the largest paired salivary glands, and is bounded by the zygomatic arch superior, the external auditory canal posterosuperiorly and the styloid process posteroinferiorly. The gland is subdivided into a superficial and deep lobe by the mandibular ramus. The facial nerve and its branches pass through the gland. The parotid duct emerges from each gland, runs through the buccinator muscle, and then opens into the mouth opposite the second maxillary molar.

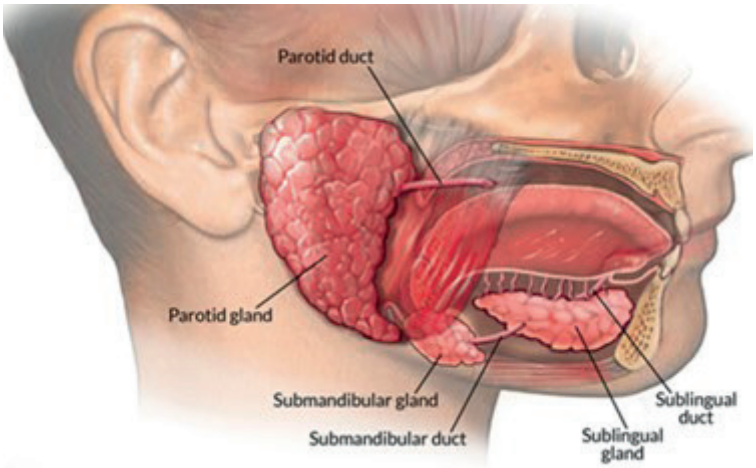


Figure 1. The major salivary glands.

About the (surgical) treatment of drooling

Surgery has been a mainstay in the treatment of drooling for several decades, despite the perceived risks associated with the different procedures. In the mid-late 1960s, the first procedure for drooling was described by Wilkie. He described bilateral relocation of the parotid duct with bilateral excision of the submandibular glands. The procedure was of great success, but with significant morbidity (duct stenosis, parotid swelling, dental or gingival problems, xerostomia, and wound dehiscence). [16] This eventually led to a modified Wilkie procedure: parotid duct ligation (rather than relocation) with excision of the submandibular gland. [16-19] To date, we know that parotid duct surgery is associated with an increased complication rate (i.e., xerostomia, parotitis) and moreover; the approach of solely submandibular gland surgery adds the possibility of revision procedures in a more personal and stepwise matter.

Patients with bothersome drooling are usually primary non-surgical treated (such as oral motor therapies and behavioral interventions (self-management) to increase awareness and swallowing frequencies, and pharmacological interventions (i.e., anticholinergic drugs) to reduce saliva. [4 20] More invasive surgical interventions are considered when conservative approaches have failed, when drooling is so severe that conservative measures are unlikely to achieve a satisfactory outcome, or when compliance with conservative measures is challenging. In anterior drooling, we try to postpone surgical interventions to an age at which we expect the normal development to have reached its limits. In general, surgery is considered after the age of 12 years. In case of posterior drooling, earlier intervention is sometimes necessary though. The overall treatment goal is a reduction of the visible spill of saliva or/and a decrease of signs and symptoms of posterior drooling.

Invasive interventions include: 1) intra-glandular injection with botulinum neurotoxin type-A (BoNT-A) or 2) surgery, which are submandibular and/or parotid duct ligation (1-4 DL), submandibular duct

relocation with sublingual gland excision (SMDR), and bilateral submandibular gland excision (SMGE).[21] Surgical intervention aims to redirect saliva by rerouting salivary flow, or to reduce salivary flow by ligation of the different ducts or eliminating saliva production by excising the submandibular gland. When operating on the submandibular gland, this involves dissection by a transcervical (mostly performed), transoral or endoscopic approach. Considering the anatomy, structures at risk of injury are the facial artery and vein, the overlying marginal mandibular branch of the facial nerve, and the hypoglossal and lingual nerves medially.[22]

About a multidisciplinary approach – Saliva Control Team

Since 2000 a multidisciplinary saliva control team has been formed at the Radboud university medical center, because we noticed the treatment of drooling can be really challenging which justifies a multidisciplinary approach. Our team included an otorhinolaryngologist, a pediatric neurologist, a pediatric rehabilitation specialist, a psychologist, and most important dedicated speech-language therapists. Parents have a key role as the primary caregivers in the process of 'shared decision making', a collaborative process through which a clinician supports a patient to decide on their treatment. In this process, we bring together our evidence-based practice refined by ongoing research, and the parental/caregiver's perception of best practice (personal circumstances, motivation, values, and beliefs).

After the initial presentation at our outpatient saliva control clinic, patients are monitored before and after intervention (if proposed). This multidisciplinary, structured evaluation offers us the possibility of delivering evidence-based medicine and to develop new strategies and research projects.

Rationale of this thesis

Drooling is an under-estimated problem, and it is often thought that compared to the other co-morbidities children with neurodevelopmental disorders cope with, it is a minor hindrance. From clinical practice, we can state that this is not the case.[23,24] Based on the principle of 'growing into a deficit,' which means children with cerebral palsy suffer from ongoing deterioration, children might suffer from even more severe drooling over the years. This underlines the need for a treatment with long term effects.

Although significant progress in the treatment of drooling has been made, there are still substantial unclarities. Unfortunately, there is no true consensus on the position and role of the diverse surgical interventions for the treatment of drooling, nor is there clarity about the submandibular gland's role within the treatment spectrum of drooling. Hence, prompting the need for further research.[4] Extensive literature suggests that surgical management using various techniques provides relief in approximately 80% of children with drooling.[25-27] A recent meta-analysis, however, stated that the results are of low evidence and heterogeneous.[27,28] That is why since 2001, at our clinic, several PhD projects have been completed addressing the different aspects and interventions for drooling to clarify the surgical indication, effects, and risks of each therapy.

In this thesis, we address the position of the submandibular gland, in particular bilateral submandibular gland excision (SMGE), in the treatment spectrum of both anterior and posterior drooling. We also address two other, less invasive treatment strategies: ligation of the submandibular ducts (2-DL) and botulinum neurotoxin injections (BoNT-A). We tried to find out whether SMGE can serve as a salvage procedure in case of residual drooling after initial surgery, and speculate on other factors that could influence success, for example the parotid glands.

This thesis also highlights the importance of posterior drooling, and we describe lessons learned by our multidisciplinary team over the years. Finally, we look at SMGE in a historical perspective of our saliva control team which has been active for over 20 years now.

OUTLINE OF THE THESIS

With a focus on clinical applicability, the aim of this thesis is the evaluation of various clinical outcomes of the surgical submandibular gland approaches for severe anterior and posterior drooling.

Chapter 1 reports a first impression of the objective and subjective results on diminishing anterior drooling in 26 children. Over the years we gained more experience with bilateral submandibular gland excision and a subsequent study was performed to investigate long-term effects and explore an update of the results in a larger sample size. These results are presented in **chapter 2**.

Since there are different approaches for bilateral submandibular gland excision (i.e., minimal invasive - endoscopically or transcervical) and the standard alternative techniques (submandibular duct ligation or relocation) are transoral, we evaluated the influence of the external scar due to the transcervical approach in **chapter 3**.

Chapter 4 is a large-scale prospective study of 57 children to establish the effect of submandibular duct ligation (2-DL) in comparison to the temporary effect of submandibular botulinum neurotoxin type A (BoNT-A) injections.

In **chapter 5**, we focus on identifying patients who underwent salvage surgery, because they were not successfully treated with submandibular duct surgery. This chapter gives us also the opportunity to speculate about the role of the parotid gland in drooling.

The last two chapters focus on lessons learned from our multidisciplinary approach over the years.

Chapter 6 of this thesis highlights the underestimated problem of posterior drooling and discusses the role of interventions on the submandibular gland in this matter. In this chapter we propose a more aggressive reduction of saliva by invasive treatment of the submandibular gland.

Chapter 7 of this thesis highlights all the efforts and lessons learned based on the evidence gained by our saliva control team over a more than 20-year period of time.

A summary and general discussion completes this thesis. Here we discuss our findings' relevance and clinical implications and provide suggestions for future research.

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Chapter 1

Bilateral submandibular gland excision for drooling: Our experience in twenty-six children and adolescents

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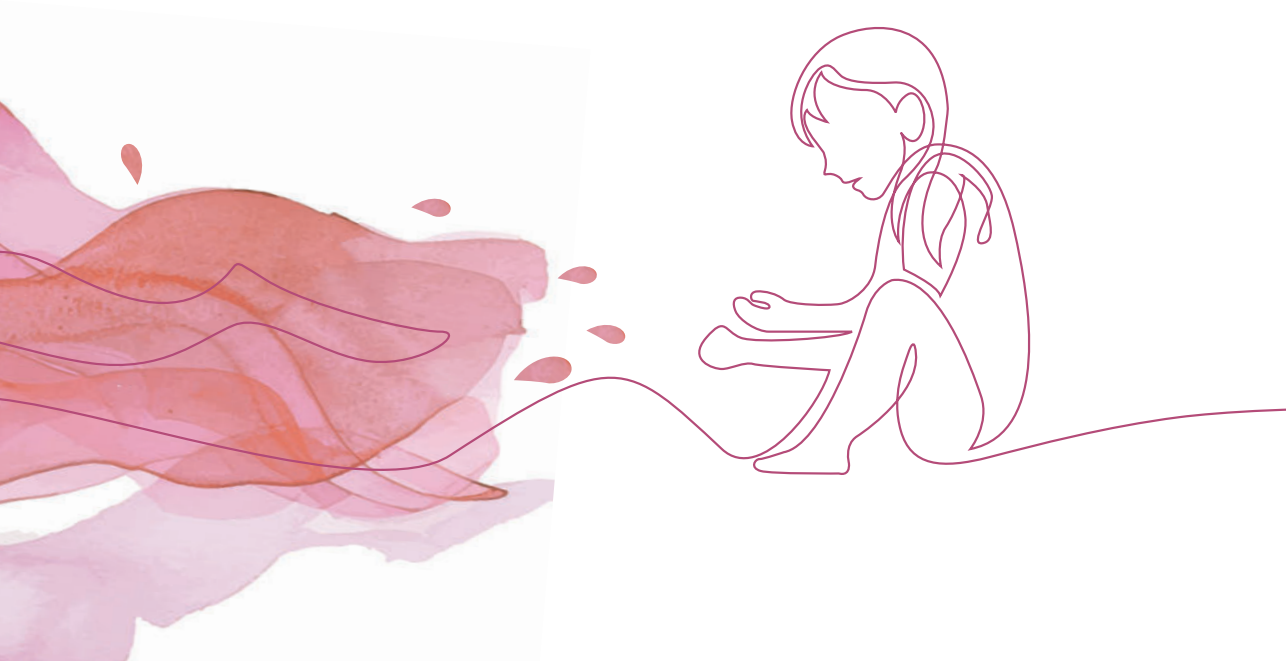

INTRODUCTION

Approximately 40% of children with cerebral palsy (CP) suffer from drooling, and it is considered severe in 15%.[1] Drooling is caused by a combination of several factors such as diminished awareness to swallow, poor posture and dysfunctional oral motor functions.[2]

We distinguish between anterior and posterior drooling. Anterior drooling is characterized by saliva spilled from the mouth that is clearly visible. Posterior drooling is defined as the spill of saliva over the tongue through the oropharyngeal isthmus, causing aspiration and associated pneumonias.[3]

Morbidity due to drooling has been widely described. Different therapies have been reviewed,[4,5] but there is no consensus regarding the optimal treatment strategy. Surgical interventions are indicated when conservative measurements have failed, when a more long-term solution is desirable or when conservative measurements are not expected to improve drooling, for example in older patients or patients suffering from a progressive disease.

In individuals with combined anterior and posterior drooling, submandibular duct relocation is contraindicated. Bilateral submandibular gland excision may be an effective procedure instead. Previous studies regarding the efficacy of this procedure were based on small and heterogeneous populations.[4–6] In particular, no validated objective measurements were used. A previous meta-analysis compared different surgical intervention methods, but did not include studies on submandibular gland excision without parotid duct rerouting or ligation.[5]

We aim to be the first to provide both objective and subjective results of bilateral submandibular gland excision in young people with neurological disabilities who drool due to severe dysphagia.

MATERIALS AND METHODS

Ethical considerations

The research was conducted in accordance with national and international ethical standards. Informed consent was provided before each intervention.

Study design

We analysed a historic cohort of children and adolescents who were examined at the Multidisciplinary Saliva Control Centre of the Radboud University Medical Centre Nijmegen, the Netherlands, between January 2001 and January 2014. Demographic data were collected preoperatively.

Surgical procedure

For submandibular gland excision, a skin incision of ≈5 cm in length was made under general anaesthesia, 4 cm below the border of the mandible. The platysma muscle was separated and the lower border of the gland exposed. If necessary, the facial artery was identified and spared if possible. The lingual nerve and hypoglossal nerve were identified and spared. After gland excision, a suction drainage was routinely placed for 1 day. Intracutaneous resorbable sutures were used.

Participants

Forty-five children and adolescents have undergone bilateral submandibular gland excision. This decision was made on expert opinion by our multidisciplinary team. Subjects were categorised by CP type, having epilepsy, severity of motor disturbance assessed by the Gross Motor Function Classification System (GMFCS), posture, developmental age, ability to eat and type of drooling (Table 1).

Table 1. Patient characteristics.

	Included for analyses *n* = 26
Sex, *n* (%)	
Male	13 (50)
Female	13 (50)
Mean age at intervention, year : month (SD)	
Submandibular glands excision	15 : 6 (6.72)
Botulinum toxin-A injections	12 : 0 (6.06)
Main diagnosis, *n* (%)	
Spastic CP	11 (45.8)
Spastic/dyskinetic CP	2 (8.3)
Ataxic CP	2 (8.3)
Dyskinetic CP	2 (8.3)
Other developmental disability	7 (29.2)
Missing	2
Developmental age, *n* (%)	
<4 years	20 (87)
4–6, IQ <70	1 (4.3)
>6 year	2 (8.7)
Missing	3
GMFCS level, *n* (%)	
I	1 (4)
II	3 (12)
III	2 (8)
IV	2 (8)
V	17 (68)
Drooling kind, *n* (%)	
Anterior	10 (38.5)
Antero-posterior	16 (61.5)
Epilepsy, *n* (%)	
Controlled	18 (72)
Intractable	2 (8)
No	5 (20)
Missing	1

Table 1. Continued

Head position, *n* (%)	
Anteflexion	6 (24)
Retroflexion	1 (4)
Asymmetrical	7 (28)
Normal	9 (36)
Not registered	3 (8)
History of pneumonia, *n* (%)	
Yes	12 (46.2)
No	14 (53.8)
Use of benzodiazepine, *n* (%)	
No/unknown	24 (92.3)
Yes	2 (7.7)
Gastrostomy feeding required, *n* (%)	
Oral + feeding tube	5 (20.8)
Oral	12 (50)
Feeding tube	7 (29.2)
Missing	2

GMFCS: Gross Motor Function Classification System level descriptions; I: reduced speed, balance and coordination; II: limitations walking on uneven surfaces and inclines, and in crowds or confined spaced; III: walking indoors or outdoors on a level surface with assistance, wheelchair as needed; IV: reliance on wheelchair; V: no means of independent mobility; CP, cerebral palsy.

We excluded three cases with posterior drooling only, as drooling intensity was assessed by measuring visual saliva loss. In addition, we excluded twelve cases who had undergone surgery for drooling prior to our surgery. Three children were excluded because of incomplete or missing medical records. In one case, the period between botulinum toxin-A injection and surgery was <24 weeks. Ultimately, 26 cases were included for analysis.

Variables

Drooling was assessed at baseline and prospectively during follow-up visits in the outpatient clinic (8 and 32 weeks after treatment). Drooling intensity was evaluated using the drooling quotient (DQ), which is a validated, semi-quantitative direct observational method. The DQ is expressed as a percentage estimated from the ratio of observed drooling episodes and the total number of observations (DQ [%] = 100 x number of drooling episodes/20).[7,8] Successful therapy effect was defined as a higher than 50% reduction compared to baseline.

Severity of drooling during the prior 2-week period was scored by a visual analogue scale (VAS) score. Caretakers assign a drooling score by marking on a line from 0 (= no drooling) to 100 (= excessive drooling). A reduction of VAS score of >2 SD from baseline is considered clinically significant. The Thomas–Stonell and Greenberg classification, which consists of a 5-point scale for severity and a 4- point scale for frequency, was used as a second subjective score.

Statistical analysis

Descriptive statistics were employed to summarise patient characteristics. For DQ and VAS, univariate ANOVA with repeated measures analysis was used. The patient was set as random factor and time as fixed to evaluate whether treatment responses differed significantly over time. When significant, a *post hoc* pairwise comparison (Fisher's LSD) was performed to evaluate differences between means at different time points. Chi-squared (χ^2) test was used to confirm the association between antero-posterior drooling and recurrent pneumonias based on history. Data were analysed using SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Characteristics of the 26 patients included for analyses are shown in Table 1. Diagnoses comprised of 17 patients with CP, two patients with a yet unknown disease and seven patients with a non-progressive developmental disability.

Observation and scoring by speech therapists revealed that a minority of 39% had anterior drooling only, compared to 61% with antero-posterior drooling. Correlation analyses revealed that 19 of 25 subjects with a combination of anterior and posterior drooling had suffered from recurrent pneumonias in the past, while none of the subjects with anterior drooling alone had suffered from pneumonia (Chi-squared-test; d.f. 1: value 17.917, $P < 0.001$). This result was in accordance with the observations by the speech therapists.

The average age at the time of surgery was 15.6 years (SD 6.72, range 2–38 years). Two subjects were transferred to the intensive care unit, due to bleeding requiring reoperation. One case of xerostomia was reported. No procedures resulted in damage of the marginal branch of the facial nerve, lingual nerve or hypoglossal nerve.

Subjective outcomes based on the Thomas–Stonell and Greenberg classification are shown in Figure 1. At baseline, caregivers had assigned the highest score of 4 for drooling frequency (defined as 'constant, always wet') in 72.7% of cases. In contrast, at 8- and 32-weeks follow-up, scores lower than 4 were assigned in 87.5% and 85% of cases, respectively. Drooling severity was assigned the highest score of 5 (defined as 'profuse, hands, clothes and objects wet') by 68.2% of caregivers at baseline. At 8 and 32 weeks, this was reduced to 25% and 26.3%, respectively.

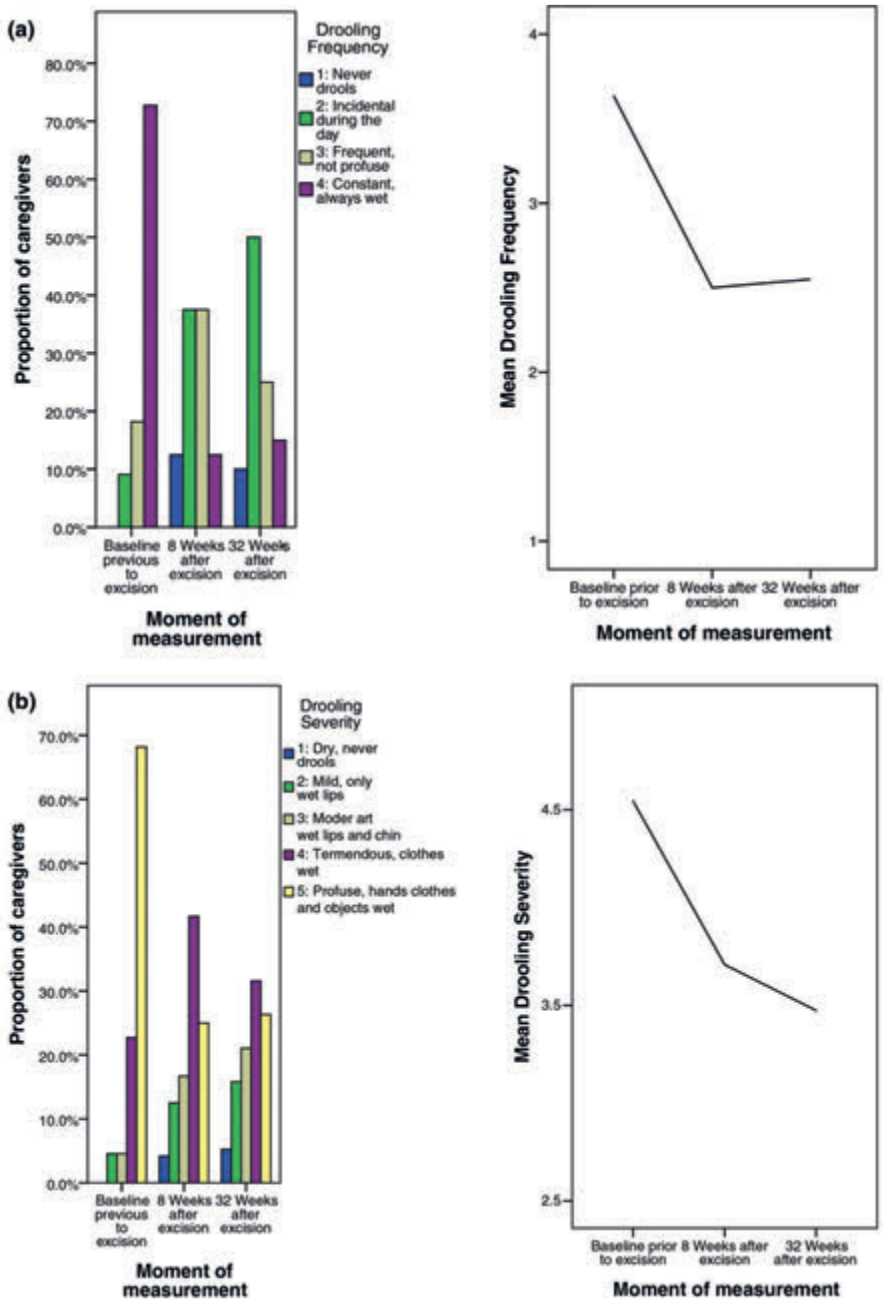

Figure 1. (a) Drooling frequency score, marked by caregivers before and after surgery. (b) Drooling severity score, marked by caregivers before and after surgery.

Univariate ANOVA with repeated measures analysis revealed a significant effect of time for both subjective VAS score ($P \leq 0.001$, d.f. 2, F 16,589) and objective DQ ($P = 0.002$, d.f. 2, F 7, 498) (Figure 2). The marginal mean DQ was reduced from 33.5 at baseline to 17.1 at 8 weeks ($P = 0.008$) and to 9.9 at 32 weeks ($P = 0.001$) following surgical intervention. The estimated marginal mean VAS score improved from 75 at baseline to 34.7 after 8 weeks. Although the mean score was slightly higher (40.5) after 32 weeks, this was still significantly lower than at baseline ($P \leq 0.001$) (Table 2). Based on the treatment success criteria, 64.7% and 61.5% of subjects had at least a 50% reduction in DQ at 8 weeks and 32 weeks, respectively. Success rates based on a VAS score reduction by at least 2 SD were 55% at 8 weeks and 44% at 32 weeks.

Sample sizes for the analysis of treatment responses varied from 18 to 23, as we did not impute for missing data.

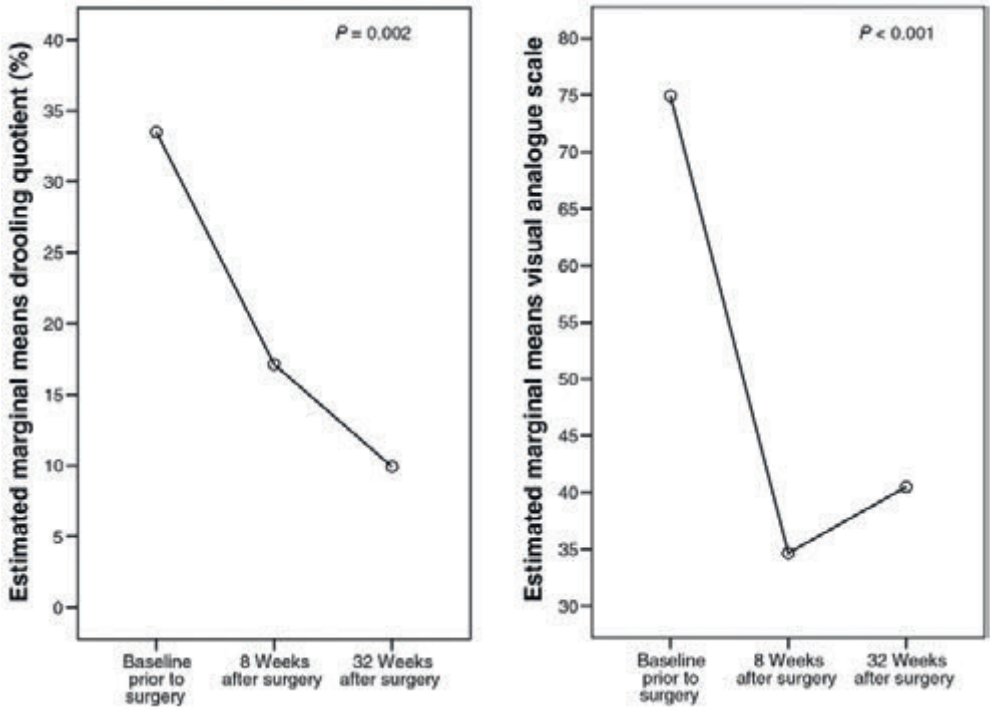

Figure 2. Estimated marginal mean drooling quotient and visual analogue scale (VAS) scores during follow-up moments.

Table 2. Mean differences between baseline and follow-up of drooling quotient and visual analogue scale (VAS).

	No. of observations	Missing observations	Absolute mean difference (95% CI)	Relative mean difference (%)	Significance (*P*)
Drooling quotient					
Baseline	21	5			
8 weeks	21	5	16.37 (4.5–28.2)	49	0.008
32 weeks	18	8	23.58 (10.6–36.5)	70	0.001
Visual analogue scale					
Baseline	23	3			
8 weeks	21	5	40.23 (25–55.6)	53.70	≤0.001
32 weeks	19	7	34.45 (18.5–50.4)	46	≤0.001

The mean difference is significant at the 0.05 level. CI, confidence interval.

DISCUSSION

Synopsis of key findings

We demonstrate that bilateral submandibular gland excision is an effective treatment for drooling, with an overall response rate of 63%. Subjective outcome measurements also showed significant improvements following surgery. We noticed the subjective improvement was slightly less after 32 weeks, in contrast to the objective results, where the effect progressed. These differences underline the importance of the use of standardized objective outcome measurements.

Comparison with other studies

Prior to surgery, patients have frequently undergone conservative treatments, with or without success.[3–5] For the last decade, botulinum toxin-A injections in one or more major glands have offered a promising and well tolerated treatment option.[3,6,9] A recent study by Scheffer *et al*.[9] using the same objective measurements methods reported a response rate of ≈50% after 8 weeks when injecting the submandibular glands. This is only slightly lower than our response rate of 64.7% after 8 weeks. However, the effect of botulinum toxin-A injections fades after 32 weeks; it remains effective in only 11.3% of cases. In contrast, bilateral submandibular gland excision resulted in a response rate of 61.5% at 32 weeks after surgery. Nevertheless, botulinum toxin-A injections come with the benefit of limited procedure-based morbidity and the fact that the temporary nature is expected. This makes it an attractive procedure in children between 4 and 8–10 years of age, when ongoing development still might solve the problem.

Bilateral submandibular gland excision is slightly less effective compared to submandibular duct relocation (response rate 81% in our clinic).[5,9] Differences in success rates can be explained by the multivariate causes of drooling and heterogeneity of the population. Submandibular duct relocation is only performed in those patients with only anterior drooling and a safe pharyngeal phase of swallowing.

Excision of the submandibular glands is also performed in those with combined or posterior drooling, and thus patients with a more pronounced severe dysphagia. In addition, submandibular duct relocation may trigger a more frequent swallowing reflex due to pharyngeal saliva release after surgery. This could explain differences in success.

Ligation of the salivary ducts has recently gained popularity.[10] As for submandibular glands excision, ligation of the salivary ducts aims to reduce the amount of saliva produced. This procedure is attractive because of its surgical simplicity and because it carries a much lower risk for unsightly scars or nerve damage. Varying results have been reported, with response rates up to 73%. Unfortunately, further procedures are frequently required due to recurrence of drooling.[10]

Strengths and weaknesses of the study

We are aware of the fact that our group is very heterogeneous, especially in term of age, nevertheless we think that this does not influence our results. In addition, the mental age showed less heterogeneity. Although we used a small number of subjects and a short period of follow-up, we did use objective measurements during follow-up instead of only subjective measurements. Also, long-lasting results are to be expected due to the nature of the intervention.

In our study, we used stringent exclusion criteria. Although we collected a historic cohort, all data were collected prospectively. Specifically, we created a cohort with an indication for treatment of either anterior or mixed antero-posterior drooling. This allows our findings to be more easily compared with future studies and to be clinically correlated to the follow-up measurements (DQ and VAS scores).

CONCLUSION

Our study shows that bilateral submandibular gland excision significantly reduces drooling in more than half of the children with a neurological disease. This procedure is especially attractive for those where submandibular duct relocation is contraindicated. In our opinion, subsequent studies should focus on larger sample sizes and posterior drooling.

Keypoints

- Drooling is a major problem in children and adolescents with neurological disorders. It has been suggested that excision of the submandibular glands may be an effective method for reduction of saliva.
- We analysed a historic cohort of 45 patients who have undergone submandibular gland excision for moderate- to-severe drooling in our clinic between January 2001 and January 2014. Twenty-six children were eligible for analysis. They were evaluated preoperatively (baseline) and at 8- and 32-weeks following surgery.
- Drooling intensity was significantly reduced following surgery compared to baseline. Drooling quotient was reduced from a baseline score of 33.5 to 17.1 after 8 weeks and 9.9 after 32 weeks ($P = 0.002$). On the basis of our success criterion, 63% of surgeries were successful. Similarly, subjective visual analogue scale score and drooling severity and frequency scores showed significant improvement following surgery.
- Bilateral submandibular gland excision is an effective therapy for drooling in young people with neurological disabilities, especially when submandibular duct relocation is contraindicated.

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1

Chapter 2

Long-term effects of submandibular gland excision on drooling in children with neurodevelopmental disorders: A cross-sectional study

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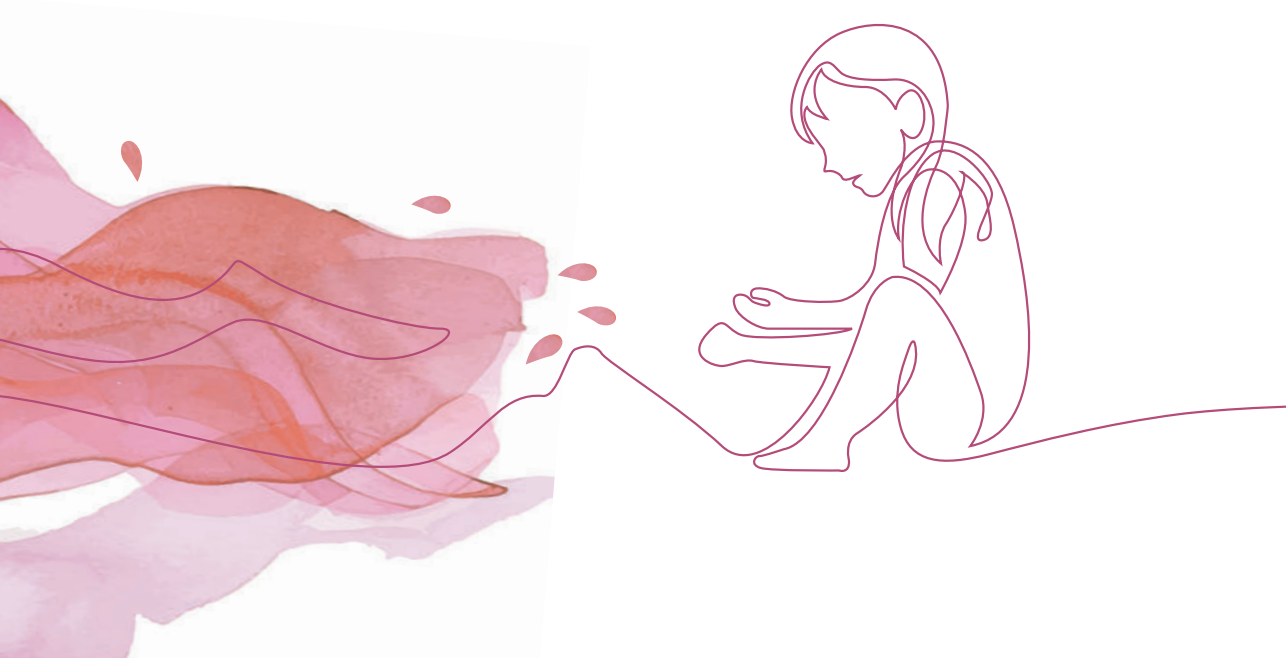

ABSTRACT

Aim

Submandibular gland excision (SMGE) is suitable for the management of drooling in patients with non-progressive neurodisabilities. We aimed to investigate the long-term effects of SMGE.

Method

Patients who had SMGE between 2007 and 2018 were included. Main outcomes were a Visual Analogue Scale (VAS), Drooling Severity (DS), and Drooling Frequency (DF) collected at baseline, 8 weeks, 32 weeks and with a median of 313 weeks after SMGE (long-term). Secondary outcomes were satisfaction with the procedure, Drooling Quotient (DQ) and adverse events (AEs).

Results

We included thirty-five patients in the long-term analysis with a mean age of 14.5 years. A baseline VAS score of 80.4 was found, which improved on the long-term (mean difference − 21.8, $t(26) = 4.636$, $p < 0.0005$)). DS and DF decreased significantly at the long-term compared to baseline ($Z = -4.361$, $p < 0.0001$ for DS, $Z = -3.065$, $p = 0.002$ for DF). Twenty-three out of 35 (66%) patients would recommend the procedure to peers.

Interpretation

This study indicates a long-term stable effect on drooling after SMGE in patients with anterior drooling. Recurrence of drooling occurs due to unknown reasons, nevertheless most caregivers and/or patients are still satisfied and would recommend the procedure to others.

INTRODUCTION

Drooling is normal in healthy infants, awaiting the development of oral neuromuscular control. Drooling is usually considered to be abnormal when persisting after the age of 4–6 years.[1–3] Neurological disorders can disturb the normal development and lead to persistent drooling. Drooling can be divided into anterior and posterior drooling, in which anterior drooling is characterized by saliva spilled from the mouth that is clearly visible. Posterior drooling is defined as the spill of saliva over the tongue through the oropharyngeal isthmus, leading to pooling, obstruction incidents and/or aspiration.[4]

There are several treatment options for drooling, which include behavioral therapy, oral motor treatment, pharmacological treatment, and surgical interventions. When conservative treatment fails intraglandular injections with botulinum toxin (BoNT-A) or surgical interventions such as salivary duct ligation, relocation and/or bilateral submandibular gland excision (SMGE), are treatment options.[5] Intraglandular injections with BoNT-A have their limitations, as the effect is only temporary.[6]

Submandibular duct relocation is a highly effective alternative procedure to diminish drooling, however, only in patients with a normal pharyngeal phase of swallowing.[7] Salivary duct ligation is a simple procedure for anterior-posterior drooling, unfortunately the recurrence rate varies between 0 and 58%.[8,9] As an alternative, SMGE is suitable for the management of both anterior and/or posterior drooling. Likely, SMGE is an intervention with potency that is a common, well-known procedure, for most otolaryngologists.

Earlier research has shown an objective effect of 61,5%, 32 weeks after SMGE.[4] To date, there are no studies that focus on the long-term effect of SMGE.

The aim of this cross-sectional follow-up study is to investigate the long-term effects and caregivers' satisfaction of SMGE in children and adolescents on anterior drooling.

MATERIAL AND METHODS

Study design and setting

A historic cohort of children and adolescents who underwent bilateral submandibular gland excision (SMGE) between 2007 and 2018 was identified. All patients were examined at the Saliva Control Team of the Radboud University Medical Centre Nijmegen, the Netherlands. The goal of our study is to evaluate long-term (>1 year postoperatively) effectiveness of SMGE in comparison to baseline, 8 and 32 weeks postintervention. Data until 32 weeks postoperatively were obtained in a prospective manner. The long-term effectiveness was evaluated based on a survey which consisted of 22 questions, filled in by the caregiver or investigator. The medical record was used to gather characteristics and adverse events.

The research was approved by our local ethics committee. All caregivers gave their informed consent for participation and publication of the results.

Participants

Patients were eligible to meet our study criteria when they experienced anterior or combined anterior-posterior drooling due to a nonprogressive neurodevelopmental disorder, for which SMGE was performed between 2007 and 2018.

Patients who underwent previous treatment for drooling or with less than 24 weeks between BoNT-A injection and SMGE were excluded, as well as those with incomplete medical records. Subjects were categorized by current age, sex, CP type, GMFCS classification, developmental age, having epilepsy, dysarthria, type of drooling, and recurrent pneumonia, as depicted in Table 1.

Table 1. Patient characteristics at time of the survey (unless otherwise specified).

Patient characteristics		
Characteristic		**Patients (n = 61)**
Age at time of SMGE, mean ± SD (range)		14.5 ± 5.4 (7–29)
Sex, n (%)	Male	34 (55.7)
	Female	27 (44.3)
Diagnosis, n (%)	Cerebral palsy	39 (63.9)
	Other	22 (36.1)
GMFCS level, n (%)* (n = 39)	I	–
	II	2 (5.1)
	III	3 (7.7)
	IV	5 (12.8)
	V	29 (74.4)
Ambulant, n (%) (n = 61)	Yes	11 (18.1)
	No	45 (73.7)
	Unknown	5 (8.2)
Drooling, n (%)	Anterior	24 (39.3)
	Anterior-posterior	37 (60.7)
Developmental age, n (%)	<4 y	45 (73.8)
	>4 y	12 (19.7)
	Unknown	4 (6.5)
Baseline measurements	VAS (SD)	80.4 (14.2)
	DS (range)	4.7 (4–5)
	DF (range)	4.6 (3–5)
	DQ (SD)	37.8 (24.5)

*GMFCS: Gross motor function classification system (GMFCS I-III are classified as ambulant, GMFCS IV and V as non-ambulant); measured for patients with CP.

After informed consent with the patients or parents of the patients, we sent a survey to all included patients to assess the long-term effect on drooling and satisfaction with the procedure.

Outcome measures

Primary outcome

The primary aim of this study was to compare the baseline Visual Analogue Scale (VAS) for severity of drooling, to the long-term VAS. The VAS was rated from a scale of 0–100, that reflected the severity of drooling during the previous two weeks as judged by the caregiver. Zero represented "no drooling" and 100 represented "severe drooling".

Additionally, the Drooling Severity score (DS) and the Drooling Frequency score (DF) (Table 2) [10] were obtained by caregiver assessment, evaluating drooling in the previous two weeks. VAS, DS, and DF were measured at the same points in time (8 and 32 weeks postoperatively), and additionally after a median of 313 [123–502] weeks.

Table 2. The subjective scoring system for drooling.[10]

	Drooling severity (DS)	Drooling frequency (DF)
1	Dry (never drools)	Dry: never drools Dry: infrequent, small amounts
2	Mild (only wet lips)	Occasionally drools (not every day)
3	Moderate (wet lips and chin)	Frequently drools (part of every day)
4	Severe (drool extends to clothes)	Constantly drools
5	Profuse (hands, tray and objects wet)	

Secondary outcome

Secondary outcomes were

1. Caregivers' satisfaction with the procedure. This was rated with a VAS for satisfaction with the procedure (0: not satisfied, 100: completely satisfied), and another VAS indicating the likelihood that a caregiver would recommend the procedure to other patients or their caregivers (0: would not recommend; 100: would definitely recommend).
2. Update on the objective results (Drooling Quotient) till 32 weeks follow-up, compared to the previous study performed in 2015 by our research group.[4] Drooling was objectively measured using the drooling quotient (DQ), which is a validated, semi-quantitative direct observational examination.[11] In this test, taken by speech language therapists, the patient is observed for 5 min, in which the presence or absence of drooling is measured every 15 s. The score is then divided by the total, resulting in a percentage (DQ [%] = 100 × number of drooling episodes/20).[4]
3. Adverse events (AEs) related to the intervention.

Statistical analysis

Descriptive statistics were used to summarize patient characteristics and analysis on adverse events and caregivers' satisfaction. Paired samples t-tests were used for the continuous variables. In addition, we calculated effect sizes (Cohen's D). For the DS/DF a Wilcoxon signed-rank test with Bonferroni correction was conducted. The level of significance was set at $p \leq 0.05$.

Ethical considerations

The research was conducted in accordance with national and international ethical standards. Informed consent was provided before each intervention.

RESULTS

This historic cohort included 61 patients who underwent SMGE. Twenty-six patients and/or caregivers were not available for the long-term follow-up, 3 patients deceased, 11 patients were excluded because of incomplete contact details, 12 patients and/or caregivers declined to participate for different reasons. After all, out of 61 patients 35 were included in the analyses of long-term effects because they responded to the questionnaire.

The median follow-up time was 313 weeks (IQR 233). Of the patients 55.7% was male and 44.3% female, with an average age at the time of surgery of 14.5 years (SD 5.4, range: 7–29). Forty-five patients (73.8%) had a developmental age of <4 years. Combined anterior-posterior drooling was present in 60.7% of the patients, and anterior drooling in 39.3% of the patients (Table 1).

Primary outcome (n = 35)

VAS for severity of drooling

Overall the VAS improvement in the long-term diminished slightly but remained significantly with a large effect size (mean difference − 21.8, $t(26) = 4.636$, $p < 0.0005$, Cohen's D 0.89). Also, after 8 and 32 weeks the VAS improved significantly (mean difference respectively - 39.1 (CI 31.8–46.4, Cohen's D 1.54) and − 32.4 (CI 23.6–41.2, Cohen's D 1.05) ($p < 0.0005$)). Compared to 32 weeks the long-term effect slightly increased this was not significant (Fig. 1).

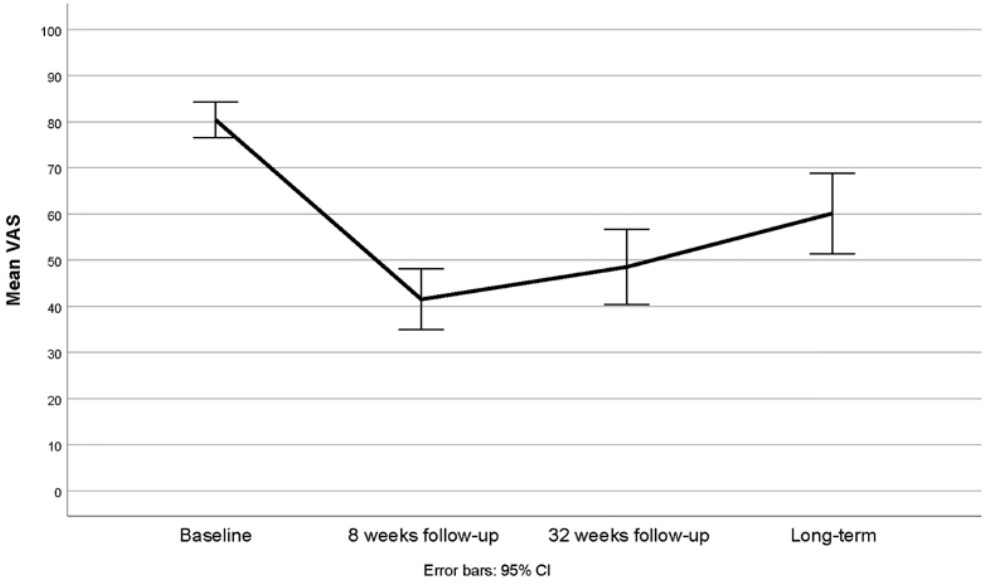

Figure 1. The mean visual analog scale (VAS) on the four different timepoints. VAS in the long-term diminished slightly but remained significantly with a large effect size (mean difference – 21.8, t(26) = 4.636, p < 0.0005, Cohen's D 0.89). Baseline compared to 8 and 32 weeks was also significantly (mean difference respectively - 39.1 (CI 31.8–46.4, Cohen's D 1.54) and – 32.4 (CI 23.6–41.2, Cohen's D 1.05) (p < 0.0005)).

Drooling severity and drooling frequency

A Wilcoxon signed-rank test showed that on the long-term SMGE does elicit a statistically significant change on drooling severity and frequency ($Z = -4.361$, $p < 0.0001$ for drooling severity, $Z = -3.065$, $p = 0.002$ for drooling frequency). In addition, results on drooling severity and drooling frequency corresponded to the VAS measurement after 8 and 32 weeks compared to baseline (both decreased significantly). Compared to 32 weeks the long-term score on drooling severity slightly decreased (less drooling), this was not significant. Nevertheless, the score for drooling frequency on the long-term compared to 32 weeks increased (more frequent drooling) significantly ($Z = -2.029$ $p < -0.042$) (Fig. 2a and b).

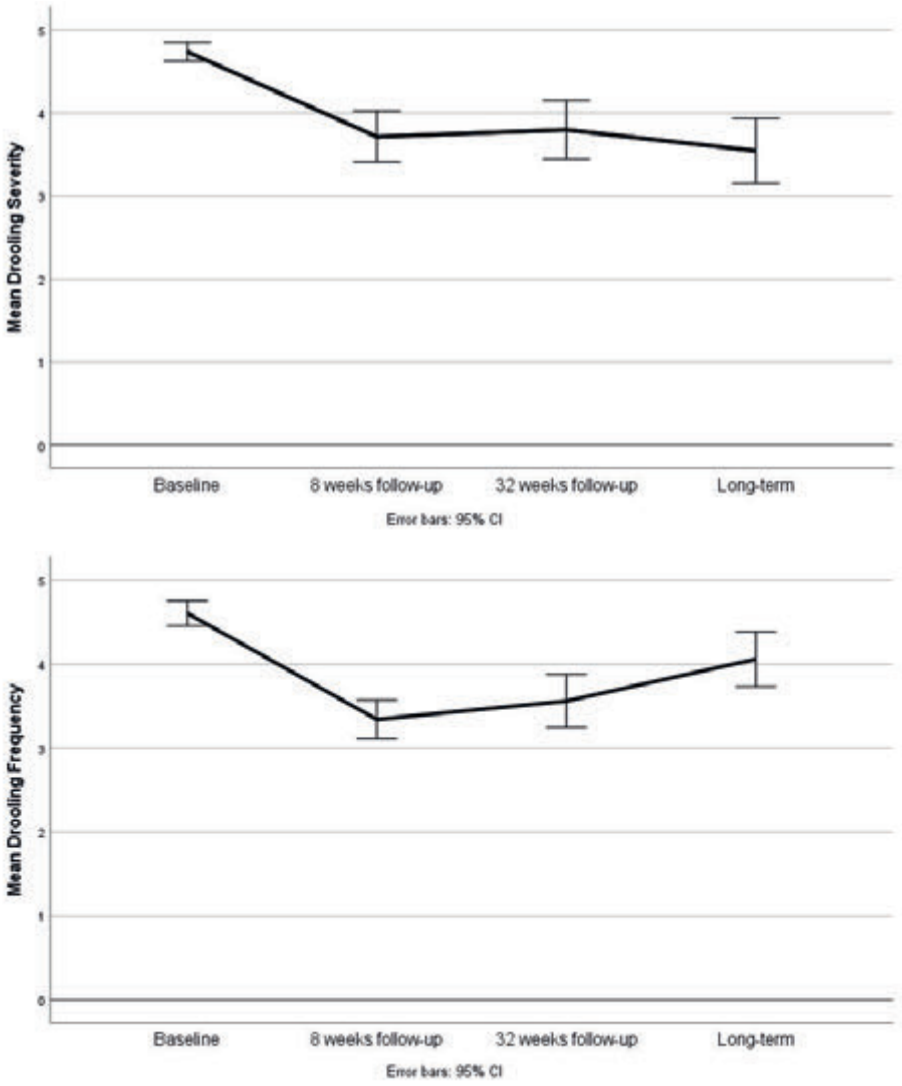

Figure 2 a and b. The mean drooling severity (DS) and drooling frequency (DF) on the four different timepoints. Based on Wilcoxon signed-rank test: significant effect on the long-term on drooling severity and frequency ($Z = -4.361$, $p < 0.0001$ for drooling severity, $Z = -3.065$, $p = 0.002$ for drooling frequency). Baseline compared to 8 and 32 weeks also decreased significantly. Drooling frequency on the long-term compared to 32 weeks increased (more frequent drooling) significantly ($Z = -2.029$ $p < -0.042$).

Secondary outcome

Long-term caregivers' satisfaction

Out of 35 patients, 23 patients (66%) would recommend the procedure for drooling, 7 patients would not recommend the procedure (6 because of diminishing effects on drooling, 1 because of disappointing effects in combination with the external scars) and 5 caregivers could not answer this question because they were not involved during the time of the procedure or were neutral. VAS for satisfaction (0: entirely unsatisfied, 100: completely satisfied) scored a mean of 74.8. VAS for recommendation of SMGE scored a mean of 71.1. From the 35 patients that filled in the survey, 6 (17%) received additional treatment (2 botulinum neurotoxin injections, 2 anticholinergic drugs, 1 combined botulinum neurotoxin injections with anticholinergic drugs and 1 radiotherapy on the parotid glands).

Drooling quotient (DQ) on the short-term (n = 61)

The objective DQ improved from 35.6 at baseline to 13.1 and 19.8 at 8 and 32 weeks respectively. Significance was found both between baseline and 8 weeks postoperatively (mean difference 22.5, CI 15.1–29.9, $p < 0.0001$) and 32 weeks postoperatively (mean difference 16.8, CI 9.1–28.5, $p < 0.0001$) after surgery.

Adverse events

Different complications occurred after SMGE. Two patients had a bleeding episode postoperatively, 1 patient had postoperative fever without a focus, and 1 patient had pneumonia. After discharge, 3 patients had a pneumonia which was treated with antibiotics, 1 patient had bleeding gums, 1 patient experienced an anamnestic increase in dental plaque, 1 patient had thick saliva, and 1 patient had xerostomia and developed more caries on the long-term.

DISCUSSION

This study evaluated the long-term effect of SMGE on drooling in patients with a nonprogressive neurodevelopmental disorder.

In this cross-sectional study we showed that bilateral submandibular gland excision led to a significant decrease and large effect size in VAS and Drooling Severity and Frequency score in patients with neurodisabilities with a mean age of 14.5 years. Compared to our previous study, the current study evaluated a larger group of patients for a longer follow-up period. The success rates of our previous study are in line with the current results.[4]

We also found a significant effect of bilateral submandibular gland excision (SMGE) on the long-term (313 weeks postoperatively). Drooling frequency increased significantly in the long-term when compared with the measurement at 32 weeks indicating some amount of recurrence. A total of 6 patient (17%)

received additional therapy. At the long-term 66% of the caregivers would recommend the procedure to others.

Our findings are in line with the results of *Bekkers* et al.[12] They found a significant effect of bilateral submandibular duct ligation (2-DL) on the long-term. In contrast with our results, they found a significant decrease of the effect, displayed by an increase in VAS at the long-term compared to the measurement at 32 weeks. In their study, 64% of the caregivers would still recommend the treatment, which is comparable to our results. Indicating that despite recurrence after both SMGE and 2-DL, effect is still visible and satisfactorily, and side effects are minor.

Interestingly, compatible with earlier studies, we found a small degree of recurrence. Despite several prediction studies for success after drooling surgery, we are to date unable to identify factors that could predict surgical failure. Different theories have been proposed and discussed; for example, an alternative salivary pathway, the role of the parotid- or minor salivary glands, compensatory hypersalivation and probably most important a variety of patient characteristics in a comorbid and complex patient population.[13–15]

Based on the well-known 'growing into a deficit' principle (children can be free from signs of dysfunction at early age but grow into a functional deficit with increasing age, because of the age-related increase in the complexity of neural functions) in children with cerebral palsy, it is suggested that a degree of recurrence might also be expected.[16,17]

Compared to other surgical interventions for drooling, SMGE seems to be a good alternative, especially in cases with combined anterior and posterior drooling, in which the most reasonable alternative procedure (submandibular duct relocation) is contra-indicated because of the risk of saliva aspiration. Moreover, SMGE is the only extra-oral procedure, this greatly reduces the risk of postoperatively nutritional problems and therefore it might be a promising therapy in a couple of children with vigorous hyperresponsive reactions in their oral cavity. Furthermore, another benefit of SMGE is the relative simplicity of the surgery, most otorhinolaryngologists, general surgeons or oral and maxillofacial surgeons can perform this procedure.

Study limitations

The biggest limitation of our study is the design and secondly the substantial risk of recall bias. The diversity in long-term follow-up moment and the use of solely subjective measurements on the long-term could have influenced the results. Nevertheless, it is debatable whether an objective measure (e.g., DQ) is clinically more important than a subjective outcome measure like caregivers' satisfaction with the results.

CONCLUSION

SMGE is a highly effective and simple to perform surgical procedure to reduce drooling in the short and long-term in patients with neurodisabilities. The procedure is especially attractive for those with anterior drooling when submandibular duct relocation is contra-indicated. Nevertheless, some recurrence on subjective measures occurs. Future research should focus on prediction of surgical failure, the potential role of the parotid and minor salivary glands and the influence of yet unknown patient characteristics. Based on our results we can conclude that SMGE is an effective, more permanent, extra-oral treatment option in severe and persistent anterior-posterior drooling, with a small risk of recurrence.

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Chapter 3

Bilateral transcervical submandibular gland excision for drooling: A study of the mature scar and long-term effects

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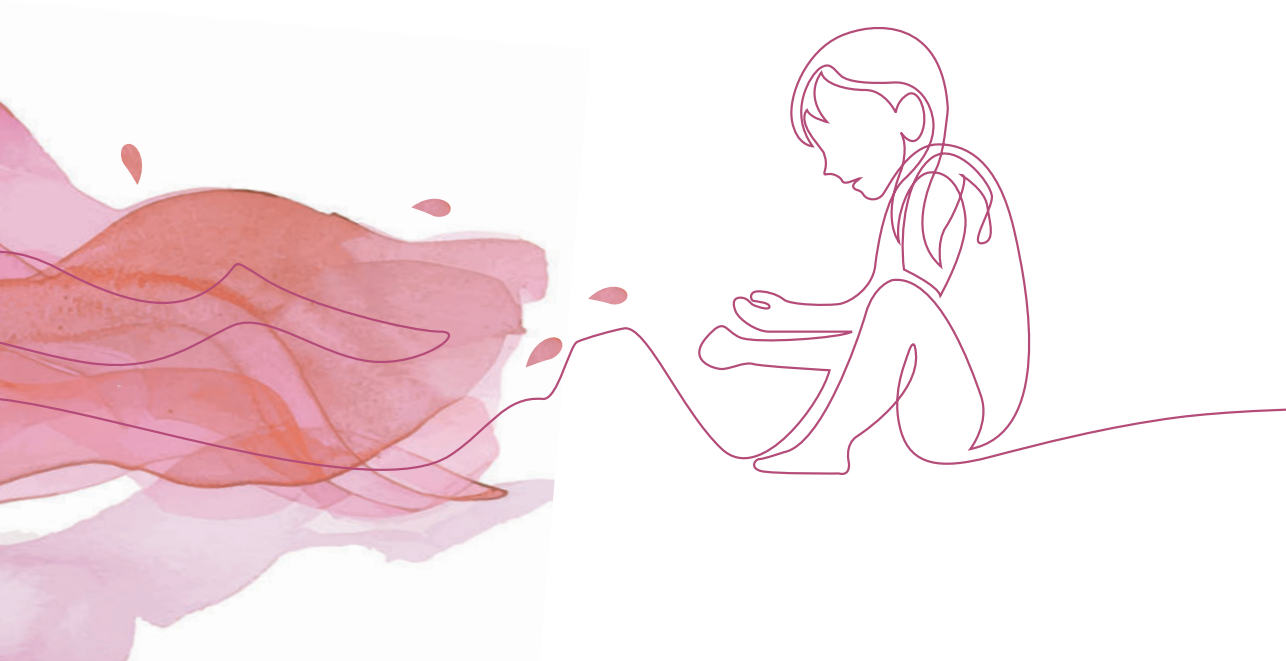

ABSTRACT

Aim

Several surgical techniques are available to treat drooling in neurologically disabled children and adolescents, with bilateral submandibular gland excision being the only transcervical procedure. External scars can be a reason to decline for this surgical approach. We investigated which factors influenced caregiver satisfaction by evaluating the long-term scar in relation to treatment outcome.

Methods

We identified a historical cohort, in which all neurologically disabled patients who underwent bilateral submandibular gland excision for drooling between January 2009 and December 2013 were identified (n = 41). The Patient and Observer Scar Assessment Scale (POSAS) was used to evaluate observer and clinician satisfaction. All included patients were contacted by telephone and completed a digital questionnaire that included digital images of the scars.

Result

Of the caregivers that responded the questionnaire 76% (19/25) were satisfied with the overall outcome. Twenty-four (96%) caregivers considered the scars acceptable. Caregiver satisfaction was not correlated to the appearance of scars, but was significantly correlated with the decrease in drooling severity on a visual analogue scale ($p = 0.035$) and decrease in lower respiratory tract infections ($p = 0.042$).

Interpretation

The appearance of scars does not influence satisfaction after bilateral submandibular gland excision for drooling. As expected, satisfaction is correlated to the treatment outcome.

INTRODUCTION

Drooling is a common problem in patients with cerebral palsy (CP) as approximately 40% of patients exhibit this symptom.[1] From a clinical point of view it makes sense to distinguish between anterior or posterior drooling. Anterior drooling is characterized by saliva spilled from the mouth that is clearly visible. Posterior drooling is defined as the spill of saliva over the tongue through the oropharyngeal isthmus, causing aspiration and associated pneumonias. Anterior and posterior drooling may occur at times in the same individual.[2]

Botulinum toxin A injections into the salivary glands has over the years emerged as an important intervention in the treatment of drooling. Botulinum toxin A inhibits the release of acetylcholine, and thereby causes temporary functional denervation of the salivary glands. This results in a reduction of salivary flow for approximately 6 months, which in most aging patients eventually leads to a surgical, more permanent, treatment.[2-4]

In the surgical treatment of drooling, an intraoral and/or transcervical approach can be employed. Intraoral submandibular duct relocation with simultaneous sublingual gland excision is currently the preferred technique for persistent anterior drooling.[5] This procedure is contraindicated in children who suffer from posterior drooling or from progressive pharyngeal dysphagia. In these patients, bilateral submandibular gland excision (SMGE) with bilateral parotid duct ligation is an alternative option.[6-8] However, xerostomia may be a problem in the combined approach, affecting 9% of the patients.[9] Therefore, we use a stepwise, less invasive surgical approach beginning with SMGE, which can be followed by treatment of the parotid glands, if drooling persists after SMGE.

SMGE is an effective treatment for drooling.[10-12] Studies investigating SMGE for other indications such as sialadenitis show that this procedure carries low risk for adjacent nerve structures and incurs little aesthetic damage.[13] Cosmetic complaints caused by damage to the mandibular branch of the facial nerve reportedly affect 0-7.7% of patients. Permanent damage to the lingual nerve occurs in 0-4.4% of patients and to the hypoglossal nerve in 0-2.9%.[13-15] Patient satisfaction with the cosmetic and long-term outcomes after SMGE to treat drooling have rarely been reported, but remains an important consideration in choosing this surgical approach, as it is the single technique using a transcervical approach.[10,11] Parent questionnaires are particularly important for evaluating the treatment outcome.[16] The Patient and Observer Scar Assessment Scale (POSAS) is an appropriate subjective tool for evaluating linear scars.[17] It encompasses three dimensions as follows: (a) physical characteristics, (b) cosmetic appearance, and (c) symptoms.[17,18] Satisfaction with scars is influenced by scar-related symptoms such as symmetry, pain and itching,[19,20] as well as by psychosocial distress, quality of life and the postoperative recovery.[20-22] Scars usually develop 6-8 weeks after epithelialization and at least 6-18 months is required for the scar to mature.[23] This period must be considered before evaluating the surgical outcome using the POSAS.

In this study, we evaluate whether the satisfaction of parents and caregivers after SMGE is influenced by the cosmetic result. Our hypothesis is that the long-term effect on drooling after surgery is the major variable influencing parental and caregiver satisfaction. We examine whether the disadvantages of surgery, including scarring, outweigh the benefits of this procedure. This is of special importance due to the vulnerability of the patient population, who are legally incapable of making medical decisions.

MATERIALS AND METHODS

Participants

Patients who underwent SMGE were recruited from the Radboud University Medical Centre Drooling database during the 5-year period from 1 January 2009 to 31 December 2013. Ethical approval for the study was granted by the Regional Ethics Committee. Informed written consent was obtained from all patients and parents or legal guardians.

Patients (children, adolescents, and young adults with a neurologic impairment) who underwent transcervical bilateral SMGE to treat drooling more than one year prior to study enrolment were included. Patients who underwent previous salivary gland surgery were excluded.

SMGE procedure

A skin incision approximately 5-cm long located 4 cm below the mandible was made under general anaesthesia. The platysma muscle was separated, and the lower border of the salivary gland was exposed. The facial artery and vein were spared if possible. The mandibular branch of the facial nerve was not identified but spared by extracapsular dissection of the submandibular gland. The lingual and hypoglossal nerves were identified and spared. Operative technique was similar for all patients, and the skin was closed in the same manner in all patients (3.0 Vicryl subcutaneously and 4.0 Monocryl intracutaneously). All procedures were performed by a single surgeon (FH). Postoperative wound management was similar in all patients and included placement of a bilateral harmonica drain for one day.

Study design

We identified a historic cohort and collected data prospectively. Parents or caregivers were contacted by telephone and instructed to complete a digital questionnaire on the cosmetic appearance of the scars, satisfaction with the procedure, complications, and the long-term effect on drooling. The questionnaire was developed specifically for this study and included a validated scar assessment questionnaire (POSAS v2.0/NL). Caregivers were asked to send a digital photograph of the scars on both sides (Fig. 1). These photographs were evaluated by a three-member panel. Clinical characteristic data were obtained from the medical records.

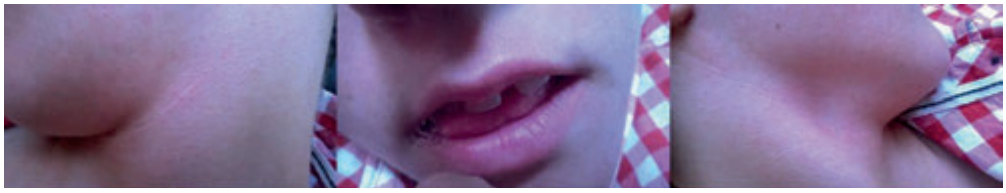

Figure 1. Digital photograph of the mouth and scars on both sides.
(published with permission)

Surgical outcome measures

As a measure of satisfaction, we asked the caregivers if they would choose the same treatment again based on the present outcome.

POSAS

Scars were assessed using the POSAS, which consists of two separate scales: a parent assessment scale (PSAS) and an observer assessment scale (OSAS). This scale was designed to subjectively evaluate various types of scars and has been proven valid for linear scars.[17,24] Caregivers were asked to respond using a numerical scale from 1 to 10 to six questions each examining the magnitude of pain, itching, color, stiffness, thickness, and irregularity of the scar. A score of 1 indicated the best possible outcome and 10 the worst. These scores were summated and yielded a maximum score of 60. The overall satisfaction with the scar was scored from 1 to 10.

During the observer panel evaluation, the photographs were randomly numbered and judged by two head and neck surgeons and an otorhinolaryngology resident. The clinicians assessed the vascularity, pigmentation, thickness, relief, and surface area of the scar. Their overall evaluation was added to scores of the specific parameters.

Drooling outcome by VAS

The subjective drooling outcome was evaluated by the caretakers using the Visual Analogue Scale (VAS) score reflecting the severity of drooling (range 0-100; 0: no drooling, 100: severe drooling) over the previous two weeks. The short-term surgical outcomes (baseline and 8- and 32 weeks postoperatively) were obtained from the medical records and compared with the long-term outcomes.

Confounding variables

As described previously, psychosocial distress, quality of life and the postoperative recovery can influence the level of satisfaction with the scars.[16] Therefore, questions about the overall postoperative recovery and changes in health status after surgery were evaluated. The caregivers were also questioned on scar-related symptoms (i.e., itching and symmetry) because these symptoms have been proven to influence the overall satisfaction.[19,20]

Statistical analysis

Descriptive statistics were employed to summarize patient characteristics. The VAS scores were analyzed using univariate ANOVA with repeated measures. The patient was designated as the random factor and time as fixed to evaluate whether the treatment response differed significantly over time.

We used the Mann Whitney U test for non-parametric data and an independent sample *t*-test for normally distributed data to determine (1) the relationship between caregiver satisfaction and the scar or treatment outcome, and (2) identify any confounding variables influencing caregiver satisfaction. Data were analyzed using SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Population characteristics

We identified 41 children and adolescents who underwent bilateral SMGE for control of drooling between 2009 and 2013. Of these 41 patients, two patients died during the study period. Another six patients had undergone previous surgery of the salivary glands for drooling (three bilateral submandibular duct relocations with sublingual gland excisions and three bilateral ligations of the parotid duct). Thirty-three patients met the inclusion criteria and were contacted by phone. Seven caregivers did not want to participate in the study. Eventually, 26 patients and caregiver pairs were sent a questionnaire. The parents or caregivers of 25 patients responded to the questionnaire and were included in the analysis. All patients had significant neurologic impairment (68% cerebral palsy). Patients exhibited anterior (28%) and antero-posterior (72%) drooling. The patient characteristics are summarized in Table 1.

The mean age at the time of surgery was 14 years (standard deviation [S.D.] 4 years and 7 months, range: 8-27 years). Postoperative wound infection or postoperative haemorrhage was not observed in any patient. None of the patients experienced xerostomia after surgery. Asymmetrical corners of the mouth were reported in three patients, likely due to paresis of the marginal branch of the facial nerve; this symptom resolved spontaneously in two patients. The marginal nerve weakness did not influence caregivers' satisfaction, as they all indicated that they would choose the same treatment again and reported to be satisfied with the cosmetic results.

Table 1. Clinical characteristics.

Characteristic	Total (n = 25)
Sex, (M/F)	13/12
Age at surgery, mean (S.D., range)	14 y 8 mo (4 y 7 mo, 8–27 y)
Follow-up duration in months, mean (S.D., range)	32 mo (15, 12–59 mo)
Primary diagnosis, n (%)	
Spastic CP	13 (52%)
Spastic/dyskinetic CP	1 (4%)
Ataxic CP	1 (4%)
Dyskinetic CP	2 (8%)
Other non-progressive developmental disability	7 (28%)
Missing	1 (4%)
GMFCS[a] level, n (%)	
I	1 (4%)
II	4 (16%)
III	2 (8%)
IV	–
V	17 (68%)
Missing	1 (4%)
Mental age, n (%)	
<4 y	18 (72%)
4–6 y	3 (12%)
>6 y	2 (8%)
Unknown	2 (8%)
Drooling type, n (%)	
Anterior	7 (28%)
Antero-posterior	18 (72%)
Previous lower respiratory tract infections due to aspiration, n (%)	
Yes	12 (48%)
No	10 (40%)
Unknown	3 (12%)
Mean VAS score at baseline, (S.D.)	79.6 (19.6)
Saliva composition at baseline, n (%)	
Seromucous	13 (52%)
Mucous	5 (20%)
Serous	2 (8%)
Unknown	5 (20%)
Days of hospitalization, median (range)	1 (1–6)

Table 1. Continued

Adverse effects	
Postoperative bleeding	0
Postoperative infection	0
Xerostomia	0
Nerve damage	
Marginal branch facial nerve, n (%)	
Persistent	1 (4%)
Temporary	2 (8%)
Lingual nerve	0
Hypoglossal nerve	0

S.D.: standard deviation; CP: Cerebral Palsy; M: male; F: female; y: year; VAS: Visual Analogue Scale (range 0–100; 0: no drooling, 100: severe drooling).

[a] GMFCS Gross Motor Function Classification Scale level descriptions; I: reduced speed, balance and coordination; II: limitations walking on uneven surfaces and inclines, and in crowds or confined spaced; III: walking indoors or outdoors on a level surface with assistance, wheelchair as needed; IV: reliance on wheelchair; V: no means of independent mobility.

Primary outcomes

After a mean follow up duration of 32 months (S.D. 15, range: 12-59) 19 of 25 caregivers replied that they would choose the same treatment again knowing the present outcome and magnitude of scarring, which indicates a satisfaction rate of 76%.

Patient scar assessment scale (POSAS)

The patient POSAS score was calculated from the sum of the individual scores for pain, itching, color, stiffness, thickness, and irregularity. The caregivers also scored according to the overall opinion of the scarring (1 indicating the best possible scar and 10 the worst scar). Parents and caregivers were very satisfied with the scars, with a mean score of 12.8 of 60 (S.D. 6.8). Most caregivers (96%) considered the scars acceptable. Among the caregivers who were unsatisfied, none of them labelled the scars as the reason. There was no significant difference between the caregiver satisfaction and the patient POSAS score (Table 2).

Observer Scar Assessment Scale

The observer scores comprised individual assessments of the vascularity, pigmentation, thickness, and area (1 indicating the best possible scar and 10 the worst scar). The scores of each parameter were summed to provide the total score. Observers also recorded their overall opinion of the scars, and the mean score of the three observers was calculated. There was no significant difference between the overall satisfaction and the observer scar assessment score, or between the observer or caregiver scores (Table 2).

Table 2. Postoperative outcomes and satisfaction reported by caregivers and observers.

	Total (n = 25)	**Satisfied n = 19 (76%)**	**Not satisfied n = 6 (24%)**	***P*-value (90% CI)**
Overall satisfaction				
Satisfied with postoperative hospital stay, n (%)				
Satisfied	21 (84%)	16 (84%)	5 (83%)	.388
Unsatisfied	4 (16%)	3 (16%)	1 (17%)	
Drooling-related satisfaction				
Drooling, n (%)				
Worse	2 (8%)	1 (5%)	1 (17%)	**.039**
Same	3 (12%)	1 (5%)	2 (34%)	
Better	20 (80%)	17 (90%)	3 (50%)	
VAS score 12-59 months postoperatively, mean (S.D.)	51.0 (36.8)	46.6 (37.3)	65.0 (34.6)	.147 (–47.9–11.1)
Change in VAS score (baseline minus long-term), mean (S.D.)	26.2 (42.1)	33.3 (43.8)	2.0 (25.9)	**.035** (3.2–59.4)
Patients experiencing fewer lower respiratory tract infections, n (%)	7 (28%)	7 (37%)	0	**.042**
Change in saliva composition, n (%)				
Thickened	13 (52%)	11 (58%)	2 (33%)	.304
Unchanged	12 (48%)	8 (42%)	4 (67%)	
Scar-related satisfaction				
Patient Scar Assessment Scale total score, mean (S.D.)	12.8 (6.8)	12.9 (7.5)	12.3 (4.3)	.433 (–5.0–6.1)
Patient Scar Assessment Scale overall score, mean (S.D.)	2.2 (1.8)	2.2 (1.8)	2.3 (1.8)	.444 (–1.6–1.3)
Observer Scar Assessment Scale total score, mean (S.D.)	11.4 (2.9)	11.5 (3.1)	11.3 (2.6)	.438 (–2.5–3.0)
Observer Scar Assessment Scale overall score, mean (S.D.)	2.5 (0.7)	2.5 (0.8)	2.5 (0.6)	.427 (–0.6–0.7)
Asymmetric scars, n (%)	7 (28%)	5 (26%)	2 (33%)	.499
Acceptable scars, n (%)				
Yes	24 (96%)	18 (95%)	6 (100%)	.411
No	1 (4%)	1 (5%)	0	

Bold values indicate statistically significance using the independent *t*-test, one-sided or the Mann-Whitney U-test ($P \leq .05$). S.D.: standard deviation; VAS: Visual Analogue Scale (range 0–100; 0: no drooling, 100: severe drooling).

Secondary outcomes

Drooling outcome - visual analogue scale

Subjective outcomes were scored using the VAS. The decrease in the VAS score, defined as the VAS score at baseline minus the VAS score at the time of the questionnaire, was calculated. Three patients did not have a baseline value, and their scores were excluded from this analysis. At baseline, the mean VAS score

of the caregivers was 79.6. At over one-year postoperatively, the mean VAS score was 53.4, indicating a reduction of 26.2 (F [1.0, 21.0] = 8.53, $p = 0.008$, 95% confidence interval [CI] 7.5-44.8) (Fig. 2).

There was no difference in the baseline VAS scores between the unsatisfied and satisfied caregiver groups. Satisfied caregivers had a mean decrease in the VAS score of 33.3 (S.D. 43.8). By contrast, the mean reduction was 2.0 (S.D. 25.9) for the unsatisfied caregivers (t[12] = 1.99, $p = 0.035$).

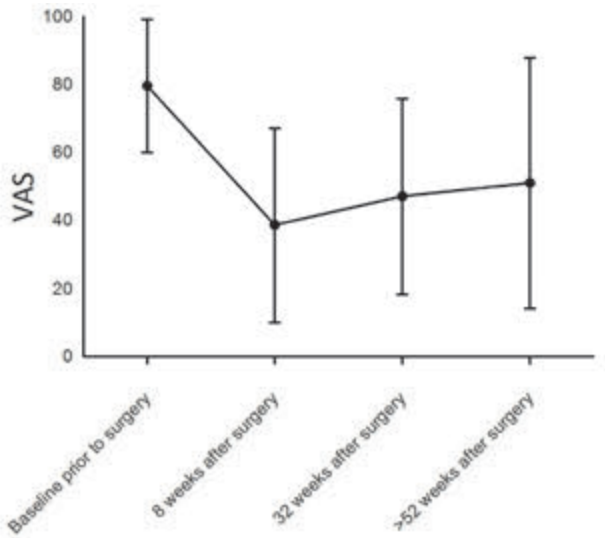

Figure 2. Mean VAS scores(•) and standard deviations(|) pre and postoperatively. VAS: Visual Analogue Scale (range 0-100; 0: no drooling, 100: severe drooling) The mean VAS score showed a significant improvement long-term (>52 weeks) compared with baseline (F [1.0, 21.0] = 8.53, $p = 0.008$, 95% confidence interval [CI] 7.5-44.8).

Lower respiratory tract infections

The medical records of thirteen patients showed lower respiratory tract infections due to posterior drooling before surgery. Of these patients, seven patients had less lower respiratory tract infections based on caregivers reports. The caregivers of those patients were satisfied with the surgery ($U = 30.0$, $p = 0.042$).

Furthermore, the overall postoperative recovery, symmetry of the scars and change in saliva composition were not correlated with the overall caregiver satisfaction (Table 2).

DISCUSSION

Major findings

The present study is the first to describe the caregivers' satisfaction after performing SMGE for drooling in children and adolescents considering both scarring and overall treatment outcome. There are several surgical treatment options for drooling, and SMGE is the only technique that produces visible bilateral transcervical scars. Nevertheless, our analyses revealed that the scars did not affect the decision to choose the same surgery again. Most caregivers considered the scars acceptable (96%); therefore, we can conclude that bilateral scars are not necessarily an objection for this procedure. In addition, SMGE is a technically simple procedure, with no major intra-operative risks and a short surgical duration and hospital stay. In our cohort, the complication rate after SMGE was very low, which is similar to previous reports.[8,11,13]

The caregivers reported an almost immediate improvement in the patients' symptoms postoperatively. The long-term decrease in the VAS score was 26.2 ($p = 0.035$). We observed a decreasing trend in the VAS score between 8 and 32 weeks after surgery, although the reduction was still significant compared with the baseline score.

Of 25 patients, two patients experienced recurrence. Recurrence of drooling may be caused by a variety of factors that can influence drooling, including an underestimation of the parotid gland activity, mouthing, poor posture and dysfunctional oral motor function. One of these two patients subsequently underwent botulinum toxin type A injections of the parotid glands.
As we hypothesized, the overall outcome after surgery was the major variable influencing parental and caregiver satisfaction. A decreased VAS score and fewer respiratory tract infections were significantly correlated with the caregiver satisfaction rate.

Comparison with previous studies

We found an overall caregiver satisfaction rate of 76%. This is comparable with the satisfaction rate reported by Stamataki *et al.* who reported a 79% satisfaction rate one year after patients underwent combined SMGE and parotid duct ligation.[25] In that study, the reason underlying the dissatisfaction was not examined. We determined the reason for dissatisfaction by asking caregivers whether the scars were objectionable, and all of the caregivers answered negatively.

In our study, one caregiver (4%) was unsatisfied with the scar result. This is comparable to the dissatisfaction rate in a normal population that underwent SMGE for benign lesions (2.5%) as reported by Springborg and Moller.[13] Previous reports describe endoscopic submandibular gland excision as an alternative choice due to the postoperative scarring.[11] Although we show that the scars are not problematic, endoscopic submandibular gland excision is disadvantaged by the cost of endoscopic equipment, the learning curve associated in mastering the technique,[26] and the 15-mm scar postoperatively.[27]

Clinical relevance

As expected, the long-term treatment outcome was the main factor influencing the parental and caregiver satisfaction. This should be considered when patients and caregivers are informed about the different treatment options for drooling. Currently, submandibular duct relocation with sublingual gland excision is the standard procedure in children with anterior drooling.[8] This procedure has the advantage of preserving the salivary gland and positively influencing the swallowing reflex. Although submandibular duct relocation is a more effective treatment in case of anterior drooling compared to SMGE,[8] it is contraindicated in patients with a progressive neurological disease or if there is a high risk of saliva aspiration and associated lower respiratory tract infections (posterior drooling).

We believe that submandibular gland excision should have an important place in the treatment spectrum for drooling, especially in those patients in which conservative treatment (e.g. Botulinum toxin A injections) options have failed or are insufficient in the long-term, and in those patients in which submandibular duct relocation is contraindicated.

Study strengths and limitations

We used a validated scar assessment scale, which in addition to gauging the observer satisfaction, also considers the satisfaction of parents and caregivers. It can be queried that we used caregivers' ratings in terms of reliability of 'pain' and 'itchiness', however these variables are important when assessing scars and we believe caregivers are the first to notice if these complaints exist. The observers performed their assessment using photographs; unfortunately, this method has not been verified. Also, using digital photographs comes with the disadvantage of variable quality of the photographs provided that could potentially influence reliability of the observers interpretation. Nevertheless, in our opinion, patient and caregiver satisfaction with postoperative scarring is more important than the opinion of the observer. We are aware that pliability, thickness, and height are important factors when rating scars, but these parameters are difficult to assess on photographs.[28] The burden for the patient to be examined in the hospital did not outweigh the desire for a verified observer score. Fortunately, the observers did not mention any difficulties with the assessment of the scars.

Seven caregivers declined to participate in the study. The reasons provided were diverse: some caregivers were too busy, another patient's health condition deteriorated. The children in this study have a low mental age (72% below 4 years), which may also have influenced the satisfaction rate. When interpreting these results, this must be taken into account. Last, the variable duration of follow-up assessment is a notable limitation. Due to the nature of the procedure, we do not anticipate that this influenced our results.

CONCLUSION

In conclusion, our study indicates that parental and caregiver satisfaction after transcervical bilateral submandibular gland excision in neurologically disabled children is not influenced by the appearance of scars, but is influenced by the therapeutic effect of the procedure. This procedure is safe, simple to perform and associated with a good long-term result.

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3

Chapter 4

Randomized controlled trial comparing botulinum vs surgery for drooling in neurodisabilities

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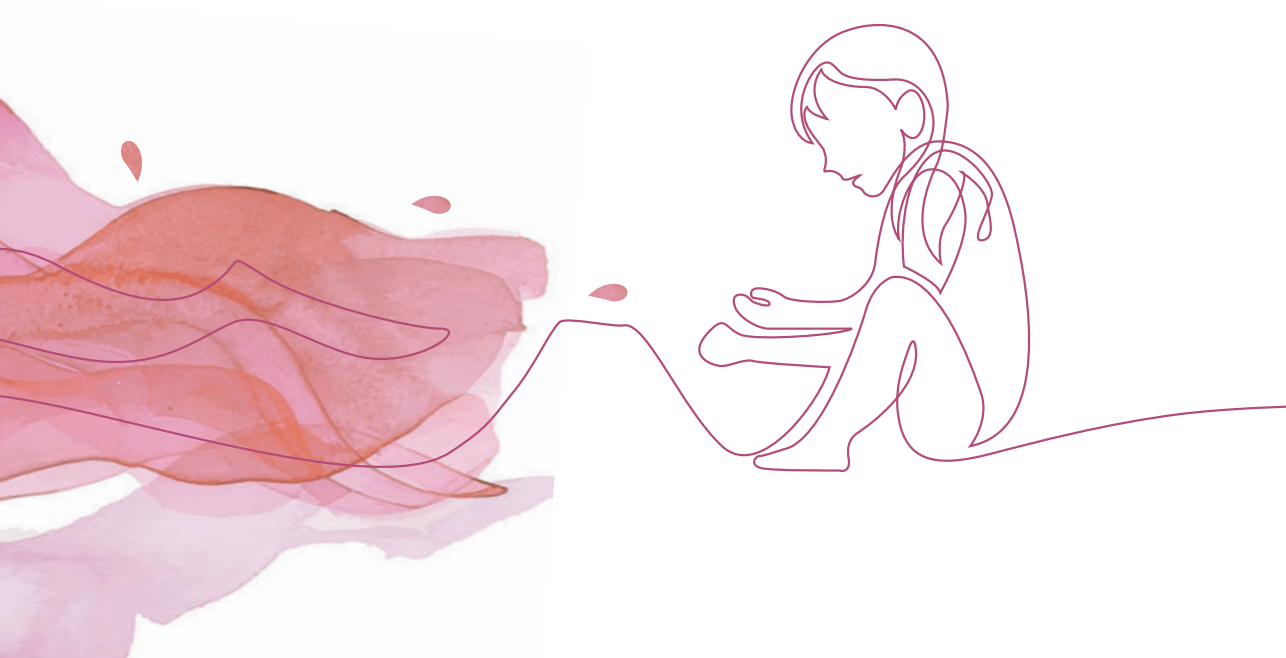

ABSTRACT

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.

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.

INTRODUCTION

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 $\chi 2$ 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).

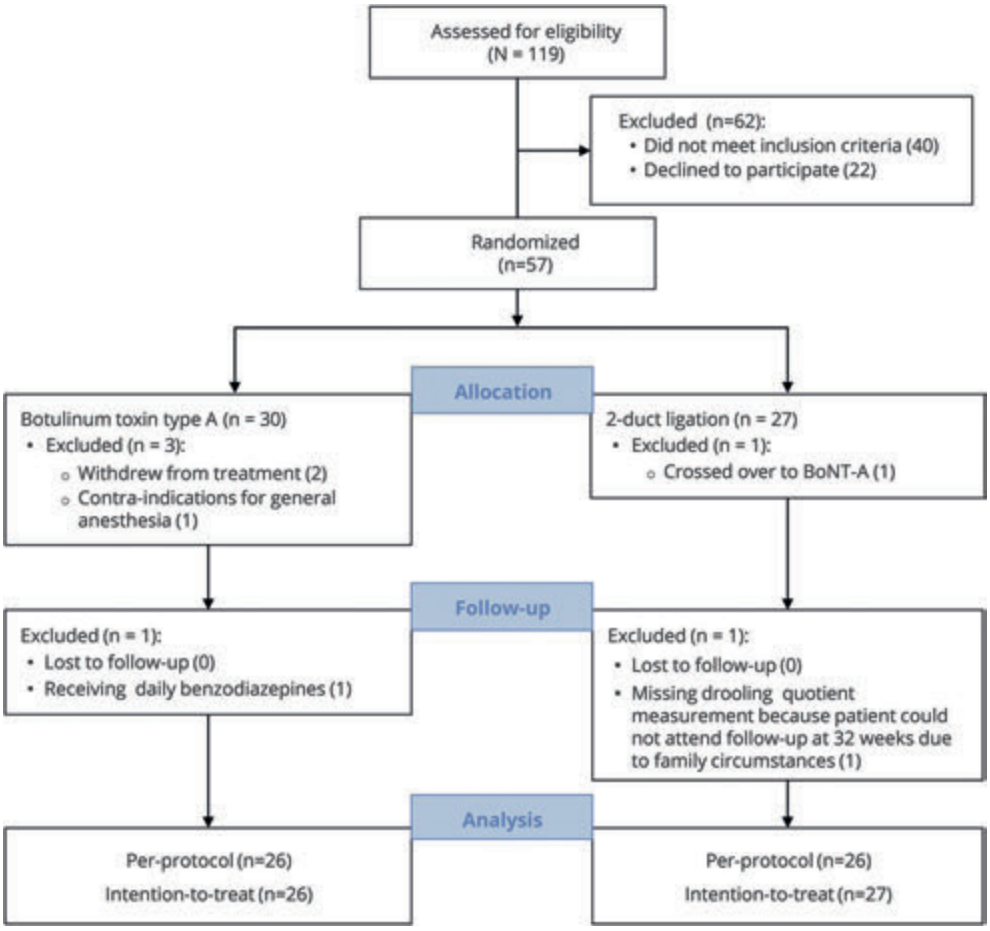

Figure 1. Flow diagram of recruited patients.
BoNT-A = botulinum neurotoxin type A.

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.

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

Table 1. Continued

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.

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 (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.

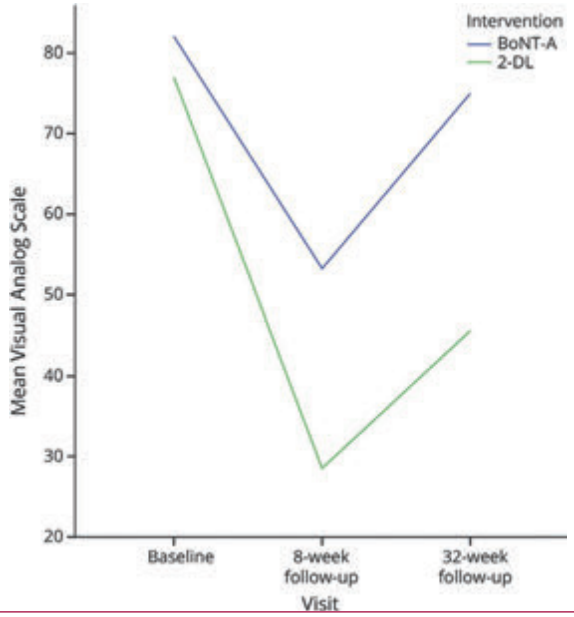

Figure 2. Visual Analog Scale.
BoNT-A = botulinum neurotoxin type A; 2-DL = 2-duct ligation.

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.

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	—	<0.001
32 wk	75.0 ± 23.0	45.6 ± 28.3	24.5 (13.2–35.7)	

	BoNT-A, n (%)					Change		2-DL, n (%)					Change	
DS	**1, Dry**	**2, Mild**	**3, Moderate**	**4, Severe**	**5, Profuse**	***z***	***p***	**1, Dry**	**2, Mild**	**3, Moderate**	**4, Severe**	**5, Profuse**	***z***	***p***
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

	BoNT-A, n (%)				Change		2-DL n (%)				Change	
DF	**1, Never**	**2, Occasional**	**3, Frequent**	**4, Constant**	***z***	***p***	**1, Never**	**2, Occasional**	**3, Frequent**	**4, Constant**	***z***	***p***
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.

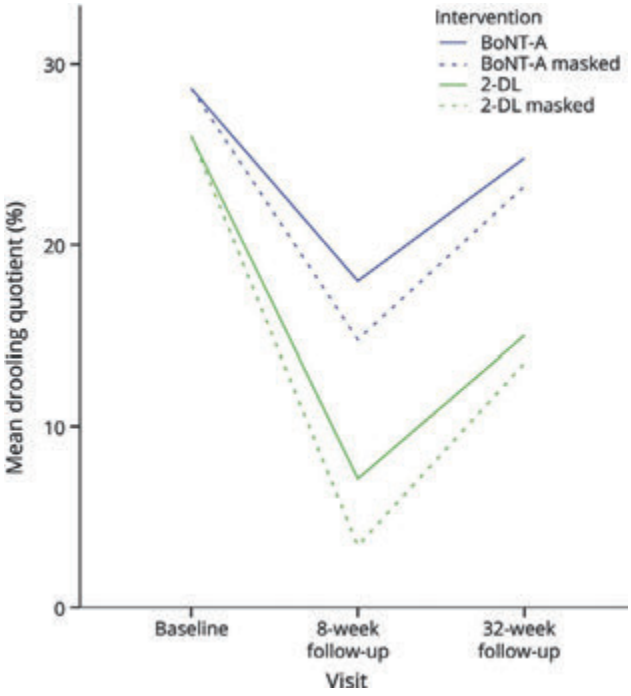

Figure 3. Drooling quotient.
BoNT-A = botulinum neurotoxin type A; 2-DL = 2-duct ligation.

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 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.

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.

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 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.

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4

Chapter 5

Unsuccessful submandibular duct surgery for anterior drooling: Surgical failure or parotid gland salivation?

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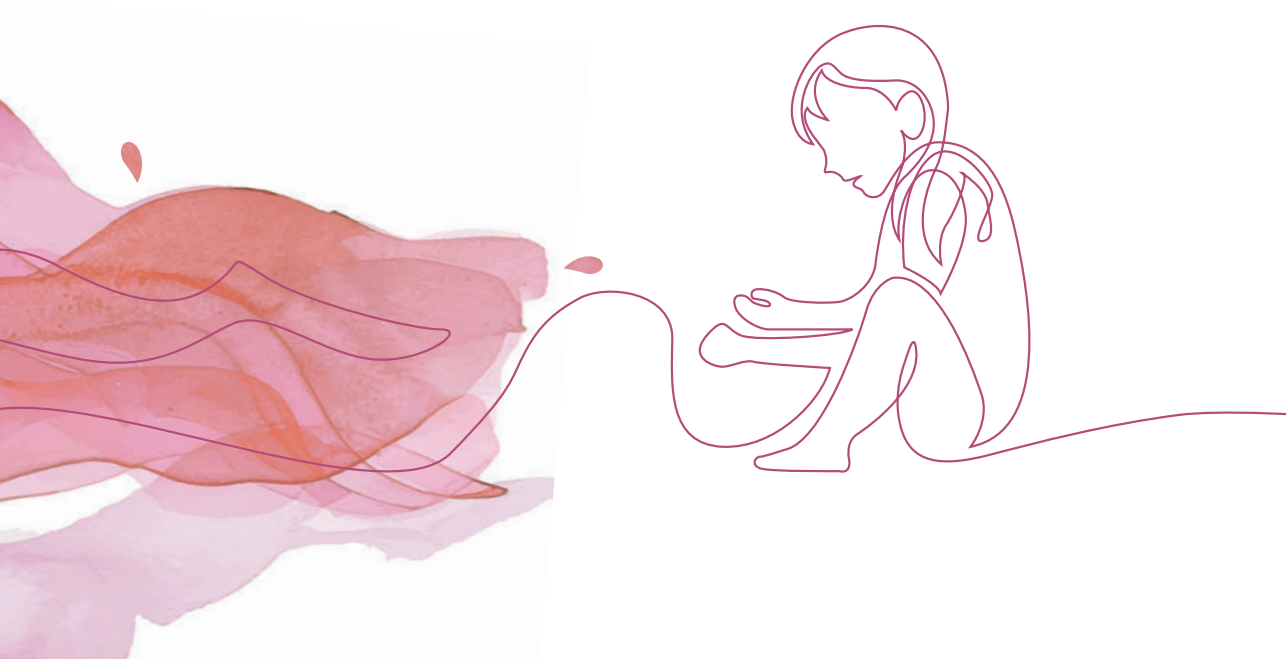

ABSTRACT

Objectives

To evaluate if drooling recurrence after surgery of the submandibular ducts is due to surgical failure or other variables.

Methods

Historic cohort with prospective collected data of all patients with severe drooling who underwent unsuccessful submandibular duct surgery with subsequent reintervention between 2003 and 2018. A reference cohort was used for comparison of clinical variables.

Results

Six males and 4 females were included (cerebral palsy n=8, neurodevelopmental disorders *n*=2). All patients underwent submandibular gland surgery as a primary intervention (duct ligation *n*=8, submandibular duct relocation *n*=2) followed by reintervention (submandibular gland excision *n*=7, parotid duct ligation *n*=3). One patient underwent tertiary surgery (parotid duct ligation after reintervention by submandibular gland excision). Three patients were successful after reintervention. No difference was found between both reintervention techniques.

There was significantly more severe dental malocclusion (50% vs. 21%, *P* value=0.047) and severe speech disorders (80% vs. 42%, *P* value=0.042) in the current cohort when compared to the reference cohort.

Conclusion

Recurrence of drooling surgery is most likely not caused by surgical failure of the primary intervention, because reintervention (submandibular gland excision) did not lead to more success. Dysarthria and dental malocclusion might negatively influence treatment outcome.

INTRODUCTION

Anterior drooling is the continuous visible spillage of saliva.[1] Although Crysdale *et al*[2] stated that drooling must be considered abnormal after the age of 4 years, a substantial part (3–15%) of the typically developing preschoolers are still drooling to a certain extent at 4 years of age. Not all these children probably suffer from pathological drooling, but drooling within a small group of children is within the range of normal variability.[3] Drooling is not caused by hypersalivation.[4] Rather, drooling is caused by a combination of several factors like diminished awareness to swallow, poor posture and dysfunctional oral motor functions (decreased peri-oral sensitivity, diminished swallow frequency, disturbed muscle tone, problems with the coordination of swallowing).[4–6] The submandibular gland produces the vast majority of saliva (65–70%) at rest, it comprises serous and mucous cells (the latter the most active). The largest salivary gland, the parotid gland, is mainly active following gustatory stimulation. It is responsible for 20% of total saliva in rest, but when stimulated this rises to over 50%. The parotid glands consist mainly of serous acinary cells.[7]

Surgical treatment is usually postponed until a later age to await a child's development.[8] Non-surgical therapeutic modalities include; speech therapy, behavioral therapy[9,10], anticholinergic drugs[11] and intraglandular botulinum toxin injections.[12,13] These therapies often bridge the gap towards surgical treatment.[14] As the submandibular glands produce the vast majority of saliva during rest, the primary focus for surgical intervention is on the submandibular glands.[15,16]

Over the years bilateral submandibular duct relocation (SMDR) with or without excision of the sublingual glands has arisen as the defacto standard surgical technique.[14,16,17] Since neurologically disabled children commonly have a dysfunctional oral phase of swallowing, relocation of the submandibular ducts to the oropharynx will enhance the swallowing of saliva. When children suffer from aspiration of saliva (posterior drooling), a combined oropharyngeal swallowing disorder, or a progressive underlying neurological condition this procedure is controversial. In these cases, duct ligation (DL) or bilateral submandibular gland excision (SMGE) are alternative techniques. Success rates of the afore mentioned procedures are generally similar (i.e. 63%–81%), with SMDR having the best results.[15,17–19] Nevertheless, a significant amount of patients after unsuccessful surgery suffer from persistent or recurrent drooling.

Recurrence or persistent severe drooling may be due to the multifactorial etiology of drooling. Although the underlying condition, use of benzodiazepines, gastroesophageal reflux disease (GERD), head posture and degree of dysfunctional oral motor control are suggested as potential influencing factors for therapy outcome, only anteflexion proved to predict surgical treatment success.[6,20,21] On the contrary, recurrence after intervention can also be due to surgical failure. For example, surgical failure of SMDR can be caused by relocating the ducts not close enough to the oropharyngeal isthmus. In addition, surgical failure after DL can be caused by e.g., failing clips or development of a collateral route.[19,22] If there is a surgical explanation of relapse after duct ligation or duct rerouting, bilateral submandibular

gland excision should theoretically solve these failures. An alternative salivary pathway formation in case of submandibular DL, or inadequate relocation of the ducts in case of SMDR as an alternative could be suspected as a cause of relapse.[19,22] However, when drooling remains refractory to reintervention with SMGE, this suggests a different mechanism. Proposed mechanisms are a compensatory salivation of the parotid glands, or a yet unrevealed predominant position of other contributory clinical variables (e.g., underlying conditions, poor posture, severe dysfunctional oral motor control).[20]

In this study, we present a case series of patients with recurrence of anterior drooling after primary submandibular duct surgery (duct ligation or submandibular duct relocation). We aimed to investigate if submandibular gland excision (SMGE) or parotid duct ligation (PDL) as a reintervention is beneficial for anterior drooling and hypothesized that either the submandibular glands (surgical failure) or underlying clinical variables (e.g., compensatory parotid salivation, lip seal etc.) are the main cause for persistent drooling.

METHOD

A historic cohort was collected of all patients undergoing a secondary surgical procedure for anterior drooling between 2003 and 2018 at the Radboud University Medical Centre. At our clinic, SMGE and PDL are considered when anterior drooling is refractory to primary submandibular duct surgery. Decision making between these two techniques is based on the expert opinion of our multidisciplinary 'Saliva Control Team', which consist of an ENT-surgeon, pediatric neurologist, rehabilitation specialist, psychologist, and speech language therapist. Changes in saliva composition (serous/mucous) and severity of drooling at rest and during activity were used in the surgical decision making. More specifically, in case of mucous saliva and drooling during the resting situation, SMGE was performed as a reintervention. On the contrary, PDL was performed when parotid gland salivation seemed to be the major problem (serous composition of saliva, drooling during activity/eating). Surgical outcomes were collected prospectively. Demographics, diagnosis, underlying conditions, and procedure(s) were obtained using clinical records from the outpatient clinic. To evaluate the potential contribution of other clinical variables, demographics and clinical variables potentially related to treatment failure (developmental age, head posture, degree of mobility, a degree of dental malocclusion[23], lip seal, Treatment Outcome Measure for dysarthria [TOM-Dysarthria[24]], Dysphagia Disorder Survey [DSS-Dysphagia][25]) were compared to a reference cohort of 122 children with CP undergoing a first submandibular BoNT-A injection.[20] We excluded patients (n=4) with missing follow-up data.

The research was approved by our local ethics committee. All patients gave their informed consent for participation and publication of the results.

Outcome measures

The Thomas-Stonell and Greenberg classification[26], which consists of a drooling severity and frequency scale, and a score on a visual analogue scale (VAS) (0: no drooling, 100: excessive drooling) for the drooling severity over the prior 2-week period were recorded as subjective outcome measures. The drooling quotient (DQ) is a validated, semi-quantitative observational method to assess drooling intensity, and served as the objective primary outcome. The DQ is expressed as a percentage estimated from the ratio of observed drooling episode and the total number of observations (DQ [%]=100 x number of drooling episode/20).[27] Response to treatment was defined as a 50% reduction on DQ or VAS at 32 weeks compared to baseline. Examinations were performed at baseline and 8 and 32 weeks after intervention.

Statistical analysis

Data were analyzed statistically using SPSS version 20.0. (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used. To analyze the overall DQ and VAS scores after reintervention we conducted paired t-test to assess differences in paired observations and conducted MANOVA with repeated measures analyses, using a within participants set-up with the measurement points as within-subject variables. Chi-squared statistics were used to compare the demographics and clinical variables to the reference cohort. A P-value of 0.05 was considered statistically significant.

RESULTS

Between 2003 and 2018 a total of 229 patient underwent surgical intervention for drooling. Reintervention for anterior drooling was performed in 10 patients (6 males, 4 females) aged between 8 and 23 years. In these patients the primary surgical therapy comprised of bilateral submandibular DL (*n*=7), bilateral submandibular DL combined with unilateral PDL (*n*=1) or SMDR (*n*=2). In seven cases surgical failure was suspected to be the cause of relapse, which led to bilateral SMGE as a reintervention. Four times the parotid glands were judged the most likely cause for relapse. In these patients unilateral (*n*=3) or bilateral (*n*=1) PDL was performed as a reintervention. In case of bilateral PDL, this was a tertiary intervention because the patient, not only experienced relapse of anterior drooling, but also suffered from severe aspiration of saliva (posterior drooling).

Demographics of all patients are shown in Table 1. The majority of patients (*n*=8) suffered from cerebral palsy (CP) with a Gross Motor Function Classification System (GMFCS) score higher than 4. Almost all patients received previous treatment with Botulinum neurotoxin type A injections more than 6 months before the primary surgical intervention. Eight patients suffered from a severe speech disorder (classified as no speech, anarthria or very severe dysarthria), and six patients were at risk for antero-posterior drooling. There was significantly more severe dental malocclusion (50% vs. 21%, *P* value=0.047) and severe speech disorder (80% vs. 42%, *P* value=0.042) in the current cohort when compared to the reference cohort (Table 2).

After primary surgery with DL the DQ initially decreased in all patients at 8-weeks follow-up, on average reducing to 18.0 (12.7) from a mean baseline value of 41.4 (15.7) but increased back to 33.3 (14.9) after 32 weeks, which was the reason for reintervention. A same pattern was observed for the VAS scores, as shown in Fig. 1A.

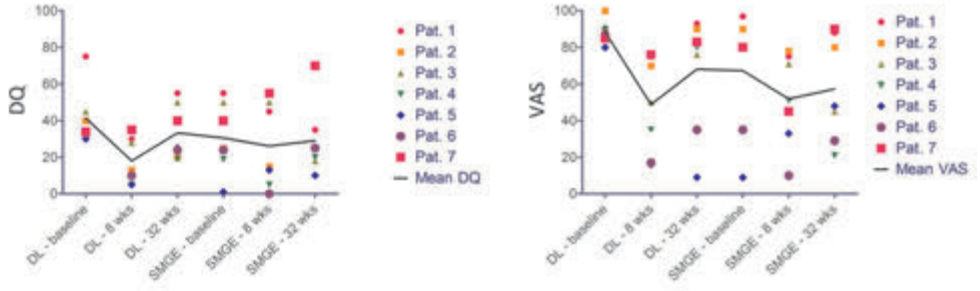

Figure 1a. Drooling Quotient (DQ) and Visual Analogue Scale (VAS) at baseline, 8- and 32 weeks follow-up, after bilateral submandibular gland excision (SMGE) as a reintervention.

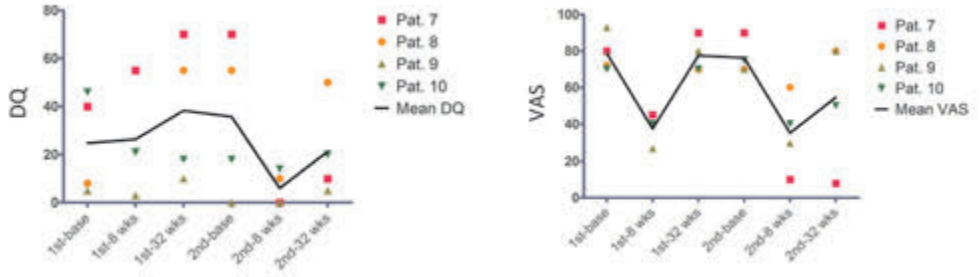

Figure 1b. Drooling Quotient (DQ) and Visual Analogue Scale (VAS) at baseline, 8- and 32 weeks follow-up, after parotid duct ligation (PDL) as a reintervention.

Table 1. Demographics.

Pat. no.	Male/ Female	Diagnosis	Comorbidity	Feeding	Mental age	Head position	Dysarthria	Drooling	Treatment before primary surgery	Surgical treatment (primary-secondary-tertiary intervention) (age)
1	F	CP: GMFCS 5 bilateral spastic	Scoliosis, GERD	Oral + feeding tube	< 4 y	Variable	Anarthria	Anterior	BoNT-A SMG (2x), BoNT-A PGL&SMG (1x)	2DL (*18 y*) -SMGE (*19 y*)
2	M	CP: GMFCS 5 bilateral spastic	Epilepsy, GERD, lower respiratory tract infections	Feeding tube	< 4 y	Missing	Anarthria	Antero-posterior	BoNT-A SMG (1x)	2DL (*21 y*) – SMGE (*22 y*)
3	F	Wolf-Hirschhorn syndrome	Epilepsy	Feeding tube	< 4 y	Normal	Anarthria	Antero-posterior	BoNT-A SMG (1x)	2DL (*9 y*) – SMGE (*10 y*)
4	M	CP: GMFCS 5 bilateral spastic	Epilepsy, bronchitis	Feeding tube	< 4 y	Variable	Very severe dysarthria	Antero-posterior	Anticholinergic medication	2DL+1PDL (*19 y*) – SMGE (*20 y*)
5	F	CP: GMFCS 5 bilateral spastic/ dyskinetic	Epilepsy, GERD	Feeding tube	4-6 y (IQ < 70)	Anteflexion	Very severe dysarthria	Antero-posterior	BoNT-A SMG (1x)	2DL (*11 y*) – SMGE (*12 y*)
6	M	CP: GMFCS 4, bilateral spastic	"Lower respiratory tract infections"	Oral	< 4 y	Variable	Very severe dysarthria	Antero-posterior	BoNT- A SMG (4x)	2DL (*15 y*) – SMGE (*17 y*)
7	M	Developmental delay not classified	Epilepsy, GERD, M. Perthes, scoliosis	Oral	< 4 y	Anteflexion	Very severe dysarthria	Anterior	BoNT-A SMG (1x)	2DL (*8 y*) – SMGE (*10 y*) – 2PDL (*10 y*)
8	M	CP: GMFCS 4, bilateral spastic	None	Oral	> 6 y	Anteflexion	Severe dysarthria	Anterior	BoNT-A SMG (1x), BoNT-A PGL&SMG (1x)	SMDR (*13 y*) – 1PDL (*20 y*)
9	F	CP: GMFCS 4, bilateral spastic/ dyskinetic	None	Oral	> 6 y	Missing	Severe dysarthria	Antero-posterior	BoNT-A SMG (1x), BoNT-A PGL&SMG (1x)	2DL (*10 y*) – 1PDL (*12 y*)
10	M	CP: GMFCS 3, bilateral spastic	Deafness	Oral	> 6 y	Normal	Very severe dysarthria	Anterior	Behavioral therapy	SMDR (*19 y*) – 1PDL (*23 y*)

GMFCS (Gross Motor Function Classification Scale level descriptions; I: reduced speed, balance and coordination; II: limitations walking on uneven surfaces and inclines, and in crowds or confined spaced; III: walking indoors or outdoors on a level surface with assistance, wheelchair as needed; IV: reliance on wheelchair; V: no means of independent mobility).CP: cerebral palsy. 1PDL: unilateral parotid duct ligation, 2PDL: bilateral parotid duct ligation, SMDR: submandibular duct rerouting, 2DL: bilateral submandibular duct ligation, SMGE: submandibular gland excision. GERD: gastroesophageal reflux disease. BoNT-A: Botulinum neurotoxin type A injections of the bilateral submandibular glands (SMG) or bilateral parotid glands (PGL).

Table 2. Clinical characteristics potentially related to treatment failure compared to a reference cohort.[20]

Clinical characteristics	Current cohort (n=10)	Reference cohort (n=122)	P value
GMFCS level IV-V, n (%)	7 (70)	77 (63)	0,75
Developmental age < 4 y, n (%)	6 (60)	63 (52)	0,75
Anteflexion, n (%)	3 (38) [n = 8]	65 (53)	0,48
Dental malocclusion, n (%)	5 (50)	25 (21)	0.047*
Incomplete lip seal, n (%)	7 (70)	74 (61)	0,74
No voluntary tongue control, n (%)	6 (60)	43 (35)	0,17
Tongue protrusion, n (%)	5 (56) [n = 9]	38 (31)	0,15
Severe speech disorder, n (%)	8 (80)	51 (42)	0.042*
DSS-Dysphagia, n (%)	4 (40)	20 (16)	0,083

Fisher's exact test is used when expected cell count is less than 5.

* = P value < 0.05; GMFCS = Gross Motor Function Classification System; GMFCS I – III is classified as Ambulant; GMFCS IV –V is classified as Non-ambulant; Developmental age<4 years vs.>4 years; Anteflexion = anteflexion head posture; Dental malocclusion = impossible clearly different vs. slightly divergent-normal; Incomplete lip seal = impossible-clearly different vs. slightly divergent-normal; Tongue protrusion: Permanent – often vs. sometimes – never; Severe speech disorder is classified as no speech, anarthria or very severe dysarthria; DSS-Dysphagia = Dysphagia Disorder Survey (Dutch version): very serious-serious vs. moderate-mild-minimal- no dysphagia.

SMGE as a reintervention after DL

When using a 50% decrease of DQ or VAS from baseline as the criterion for success, only two patients were considered successful (Table 3). Using a 50% decrease of DQ from baseline as the criterion for success, only one case could be considered successful. This was also the only patient who mentioned a decreasing drooling frequency score with a stable drooling severity score.

MANOVA of repeated measures with the DQ as the within-participants variable showed no significant pattern over time (Hotelling's trace: F=0.476; df 1, 18.; p=0.499). Furthermore, SMGE did not result in a significant reduction, from 30.6 (18.9) at baseline to 26.1 (23.0) and 29.0 (19.6) after respectively 8- and 32-weeks follow-up. Repeating the mentioned design with the VAS score as the within-participants variable also showed no significant difference over time (Hotelling's trace: F=2.546; df 1, 18; p=0.128). From a baseline value of 67.3 (32.5) the VAS score reduced to 57.3 (28.5) after 32 weeks.

PDL as a reintervention

Only the patient who underwent bilateral parotid duct ligation met the criterion for treatment success and showed a significant reduction compared to baseline in DQ (85%) and in VAS-score (91%) (Table 3, Fig. 1B). This success was also reflected in the drooling severity and frequency scale. Within subject analyses showed no significance over time for 50% decrease on DQ or VAS at 32 weeks.

Table 3. Effect on anterior drooling after reintervention.

Pat. No.	Reintervention	Change in DQ (%)[a]	Change in VAS (%)[a]	Saliva viscosity[a]	Drooling Severity[a]	Drooling Frequency[a]
Submandibular gland excision						
1	SMGE	- 20 (36%)	- 9 (9%)	Reduced	Similar	Similar
2	SMGE	0	- 10 (11%)	Similar	Similar	Similar
3	**SMGE**	**- 32 (64%)**	**- 35 (44%)**	Increased	Similar	Decreased
4	**SMGE**	**+1**	**- 59 (74%)**	Similar	Similar	Similar
5	SMGE	+9	+39	Similar	Increased	Increased
6	SMGE	+1	- 16 (17%)	Increased	Increased	Increased
7a[1]	SMGE	+30	+10	Reduced	Similar	Similar
Parotid duct ligation						
7b[1]	**2PDL**	**- 60 (85%)**	**- 81 (91%)**	Increased	Decreased	Decreased
8	1PDL	- 5 (9%)	+10	Increased	Similar	Decreased
9	1PDL	+5	+10	Similar	Similar	Increased
10	1PDL	+2	- 25 (33%)	Similar	Similar	Decreased

[1] 7a and 7b are the same patient. Patients in bold: Responder (at least 50% reduction of DQ or VAS compared to baseline). SMGE: submandibular gland excision, 1PDL: unilateral parotid duct ligation, 2PDL: bilateral parotid duct ligation. [a] At 32 weeks compared to baseline.

DISCUSSION

Surgery is the accepted "last resort" when conservative treatment options are no longer sufficient and the patient suffers from severe persistent drooling.[14–16] Several studies have assessed the efficacy of surgical procedures for drooling, with a variability in results. The reason for the differences in success after surgical interventions are unclear, theories vary from surgical failure to heterogeneity of the patient population, insufficient oral-motor control, and underestimation of parotid gland salivation.[15,17–19] To investigate the reasons for persistent drooling we evaluated 10 patients who needed reintervention because of refractory anterior drooling.

Following our success criteria (a 50% reduction on DQ or VAS at 32 weeks compared to baseline), only 3 cases (bilateral PDL or SMGE as a reintervention) could be considered successful after secondary surgery. No more than 2 (out of 11) interventions led to an objective (DQ) treatment success (Table 3). These results prove that there is limited effect of 1PDL or SMGE after 2-DL or SMDR, which strongly implies that recurrence of anterior drooling after submandibular duct surgery could not be explained by surgical failure (alternative salivary pathway formation in case of 2-DL, or inadequate relocation of the ducts in case of SMDR).[19,22]

Salivation of the parotid glands could be a compelling reason for recurrence of drooling, because bilateral PDL combined with SMGE seemed to be the most convincing treatment strategy. This finding corresponds with the limited previous literature about SMGE combined with bilateral PDL, in which this intervention showed very good subjective results as a primary intervention.[28] Nevertheless, this intervention should be handled with care, because Stern *et al.* did report a 'dry mouth' as a complication in a couple of patients. This complication could have major impact on digestion especially mastication and that in turn could have a tremendous impact on quality of life. When comparing the two patients with a DQ reduction of at least 50% with the entire group, we were unable to detect a potential source of selection bias. As displayed in Table 1, there were no major differences in characteristics. The only notable aspect was the fact that the two patients with a high therapy response, were the only patients that did not suffer from cerebral palsy and were at the lowest age at time of surgery (8 and 9 years of age at primary surgery, and respectively 8 and 10 years of age at reintervention). This is contrary to recent literature that reported age>12 years to predict treatment success after SMDR.[21]

Given the number of non-responders after secondary drooling surgery there are indications that, most likely due to all the influencing clinical variables, prediction of therapy outcome is very difficult. As displayed in Tables 1 and 2, our patients suffered from; severe neurological impairment, epilepsy, gastroesophageal reflux disease (GERD), poor posture, suboptimal dental occlusion, incomplete lip seal and poor oro-motor control. These factors are inevitably related to anterior drooling and in addition, we found that the patients in this study suffered from dysphagia and significantly more dental malocclusion and severe speech disorders (classified as no speech, anarthria or very severe dysarthria) which potentially negatively influences therapy outcomes and contributes to refractory anterior drooling despite a thorough reduction in salivary flow.[6,20] This is in line with Franklin *et al*[29] who already described in 1996 the relevance of dental occlusion in relation to drooling. In addition, Reid *et al*[6] found a relation between limited speech and drooling and concluded that poor oromotor function was associated with drooling. Cerebral palsy associated with reduced oral muscle tone and preferential mouth breathing could be the cause of the identified dental malocclusion and dysarthria. Previous research has focused on trying to identify influencing clinical factors on therapy outcome after botulinum neurotoxin type A injections and SMDR. Adequate head posture and age>12 years predicted treatment success after SMDR, but unfortunately no predictors to treatment success after BoNT-A were found.[20] Also hypersalivation has been hypothesized as a reason for therapy failure, but has shown to be inconsequential in children with CP.[4]

Despite the fact that our study is retrospective and based on limited data, we provide new insights about the efficacy of surgical reintervention for drooling. We used prospectively collected objective and subjective outcome measures with a decent follow-up protocol. Martin *et al*[22] report use of technetium scanning to identify the fate of submandibular duct diversion and ligation, respectively. Nevertheless, we believe in our patient population technetium scanning is unethical as a routine 'research' procedure.

In sum, recurrence of drooling is most likely not caused by surgical failure, and it is not likely that recurrence is solely caused by increased parotid gland salivation. The latter could not be conclusively ruled out based on our data, as stated earlier by our researchgroup 'non-responders might constitute a group of clinically different children that suffer from more parotid activity'.[30] Bilateral submandibular gland excision or unilateral parotid duct ligation are both not beneficial for anterior drooling after primary surgery on the submandibular glands in this cohort. However, we did find a good result from bilateral submandibular gland excision combined with bilateral parotid duct ligation. Further research about this intervention should be encouraged but handled with care because of the post-operative risk of xerostomia and the beneficial aspects of saliva (bolus forming, dental health, immunity) in this extremely vulnerable population. Dysarthria and dental malocclusion might negatively influence treatment outcome, but future research is needed to identify clinical variables that could influence drooling and therapy outcome in a patient centered way.

Conflicts of interest

None.

Acknowledgment

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5

Chapter 6

Posterior drooling in children with cerebral palsy and other neurodevelopmental disorders

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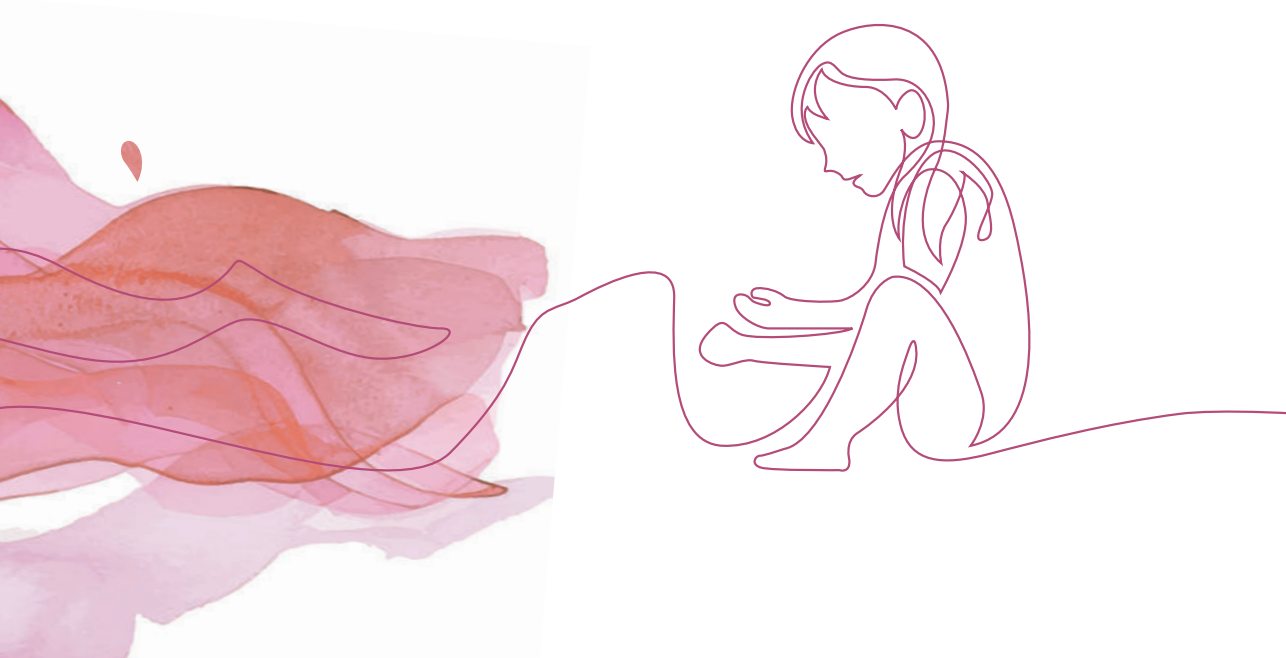

ABSTRACT

Aim

To evaluate the effect of botulinum neurotoxin A (BoNT-A) injections, submandibular gland excision (SMGE), and bilateral submandibular duct ligation (2DL) for the control of posterior drooling in children with neurological impairment.

Method

In a retrospective cohort, children with neurological impairment (e.g., cerebral palsy) treated between 2000 and 2016 were identified. Mean age at time of surgery was 9 years (range 1–21y). The primary outcome was posterior drooling severity by a visual analogue scale (VAS; 0–10) at baseline, 8-weeks, and 32-weeks follow-up. The secondary outcome was lower respiratory tract infections during the follow-up period.

Results

Ninety-two patients (out of 475; 47 males, 45 females) were identified. They were undergoing three different treatments: BoNT-A (n=63), SMGE (n=16), and 2DL (n=13). A significant reduction in VAS over time was observed in the total group of 92 patients. After SMGE, VAS decreased significantly from 6.82 (SD 3.40) at baseline to 2.29 (SD 1.93) at 8 weeks, and 2.17 (SD 2.58) at 32 weeks (F[2.34]=11.618, p<0.001). There was no significant decrease after both BoNT-A and 2-DL.

Interpretation

Posterior drooling is an unfamiliar, potentially life-threatening condition that is treatable with medication, BoNT-A injections, or surgery. Although all treatments reduced signs and symptoms of posterior drooling, there is a greater effect after SMGE compared to BoNT-A and 2-DL.

INTRODUCTION

Swallowing disorders are common in children with cerebral palsy (CP) (prevalence 50.4–99%) and other neurological impairments, and consequently these children may suffer from anterior and posterior drooling.[1] Up to 78% of the caregivers of children with CP report complaints of anterior drooling, with a mean prevalence of about 40%.[2] The prevalence of posterior drooling is unknown, but is estimated to be 10% to 15% in the population with severe or profound intellectual disabilities.

Posterior drooling is defined as the spill of saliva over the tongue into the faucial isthmus leading to pooling of saliva or saliva aspiration.[3] Normally the sensation of saliva in the hypopharynx initiates the swallowing reflex. However, when the trigger to swallow is impaired or missing, pooled saliva may lead to posterior drooling which may lead to distressing congested breathing, coughing, gagging, vomiting, and at times saliva aspiration into the trachea.[4] In children with severe oropharyngeal dysphagia, posterior drooling can lead to recurrent lower respiratory tract infections (LRTIs), progressive lung injury and obstructive episodes, associated extended hospital admissions, and pneumonia necessitating intensive care unit admission.[5] LRTIs are the most common cause of death in children with CP.[6]

The long-term effect of aspiration is dependent on multiple factors that includes the child's capacity to clear aspirated material. Bronchiectasis is a well-known sequela of chronic aspiration in children which often leads to significant morbidity.[7] Salivary aspiration due to dysphagia could therefore have a significant impact on quality of life, morbidity, and mortality.[8] Early identification and any intervention that lowers the risk of pulmonary deterioration are important to consider. Treatment options for posterior drooling are potentially diverse (e.g., anticholinergic drugs such as glycopyrrolate, botulinum neurotoxin A [BoNT-A] injections, surgery) and ideally require a multidisciplinary approach because of the multifactorial aetiology.[8,9] Initial management consists of conservative measures such as consultation with a speech and language therapist, oral hygiene advice, and oral dietary modifications (e.g., thickening liquids). To prevent aspiration, children with dysphagia are often fed by gastro- or jejunostomy. To further minimize aspiration, medical or surgical management of gastroesophageal reflux disease is important.[10] Other causes of recurrent LRTI should also be excluded. If, despite all interventions, LRTIs still occur, interventions to reduce the salivary flow are indicated.[11] Non-invasive strategies such as anticholinergic drugs may be attempted before more invasive treatments are considered.[12] In persistent or severe posterior drooling, intraglandular injection with BoNT-A or surgical intervention on the submandibular glands is indicated.[13] The submandibular glands need to be treated first, as the submandibular glands produce the majority of saliva in the resting situation.

We primarily aimed to: (1) evaluate the subjective effect of interventions for the treatment of posterior drooling in children and adolescents with neurodevelopmental disabilities and (2) decide which of the three interventions were superior. Secondary aims were to evaluate the relationship between signs and symptoms of posterior drooling and LRTI.

METHOD

Participants

Between 2000 and 2016, 475 patients visited our outpatient clinic and were identified with anterior or posterior drooling and registered in our database. A retrospective cohort study was performed after identifying all patients in our database who were diagnosed with posterior drooling between 2000 and 2016 by our multidisciplinary saliva control team. Our team consisted of a speech language therapist, neurologist, otolaryngologist, psychologist, and rehabilitation specialist.

Patients were identified when they had symptoms of posterior drooling as described by Jongerius *et al.*[4] Symptoms that should raise suspicion about posterior drooling include congested breathing, coughing, or gagging on saliva, wheezing, tachypnea, and/or episodes of fever. Demographic variables were collected at baseline. Outcomes were collected as per our standard follow-up protocol: before surgery (baseline), and at 8 and 32 weeks after treatment.

Data management and statistical analysis were carried out using SPSS 22.0 for Windows (IBM Corp., Armonk, NY, USA).

The study was approved by our local ethics committee and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Procedures

In our clinic the surgical treatment of drooling consists of a conservative personalized stepwise approach, in which we aim to minimize side effects. Adverse side effects of submandibular gland excision (SMGE) include xerostomia (dry mouth), with resulting impact on mastication and dental health, external scarring, and risk of facial and hypoglossal nerve damage. In this study we solely focused on therapeutic interventions aimed at the submandibular gland: BoNT-A injections into the submandibular gland, bilateral SMGE, and bilateral submandibular duct ligation (2DL). Submandibular duct rerouting is contraindicated in posterior drooling. The primary choice of surgical intervention is based on expert opinion by our saliva control team in which patient characteristics, for example age, oromotor functioning, and comorbidity, are very important. In our team it is generally agreed that non-invasive or less invasive strategies should be attempted before more invasive treatments are considered. That is why we reserve BoNT-A injections for patients under the age of 10 years old. For patients 10 years of age or older or patients with severe life-threatening symptoms, surgery is indicated.

All procedures were performed by the hospital's protocol as described in previous articles by our saliva control team.[14–16] The different interventions were performed by the same two specialists at all times (BoNT-A was performed by our rehabilitation specialist; 2DL and SMGE by one otolaryngologist).

Outcome

We used a caretaker visual analogue scale (VAS) as the primary outcome, to reflect the severity of posterior drooling over the past 2 weeks. It was scored on a scale from 0 to 10, with 0 corresponding with no symptoms and 10 to severe symptoms (congested breathing, coughing, or gagging on saliva).

As a secondary outcome, frequency of LRTI was recorded from 1 year before baseline, baseline to 8 weeks after intervention, and 8 to 32 weeks after intervention. This was scored based on history taking and medical record review. If the patient suffered from congested breathing, wheezing, tachypnea, and episodes of fever before the visit at our outpatient clinic, this was classified as a possible LRTI.

Statistical analysis

For analysis of the VAS, we employed descriptive statistics and performed a one-way analysis of variance (ANOVA) with repeated measures design and post hoc tests to evaluate the overall treatment response over time. For analysis of LRTI, we performed χ^2, Cochran's Q, and McNemars tests. Pearson's rho was used to study the correlation between the subjective VAS posterior drooling severity and the LRTI. Missing values (7%) in our data were imputated using SPSS Multiple Imputation. Because we found no difference in outcome between the imputed data and the original data, we decided to use the original data. A p-value of ≤0.05 was considered statistically significant.

RESULTS

Patient demographics

Ninety-two (19%) out of 475 patients (mean age 9y 6mo [1–21y]) were identified with posterior drooling between 2000 and 2016 (Table 1). Three different groups were defined: (1) BoNT-A injections into the submandibular glands (*n*=63); (2) SMGE (*n*=16); and (3) 2DL (*n*=13). Differences between groups were anticipated based on clinical selection criteria between the different interventions.

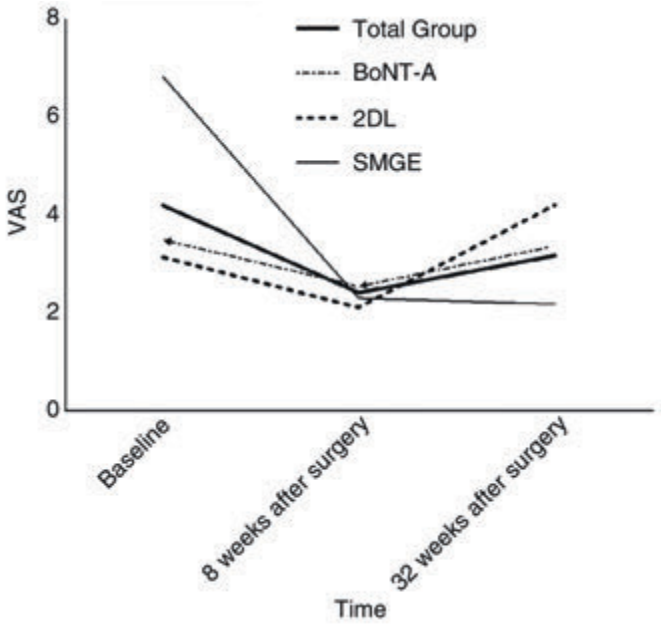

Figure 1. Mean visual analogue scale (VAS) score over time. Total group: mean VAS score was statistically significantly lower after 8 weeks (p=0.004) compared to baseline. Submandibular gland excision (SMGE): mean VAS score was statistically significantly lower after 8 weeks (p<0.001) and 32 weeks (p<0.001) compared to baseline. BoNT-A, botulinum neurotoxin A; 2DL, submandibular duct ligation.

Primary outcome

VAS – total group

The mean VAS posterior drooling severity of the total group declined by 44% after 8 weeks and 25% after 32 weeks. The VAS score declined from 4.19 (SD 3.25) at baseline to 2.40 (SD 2.42) and 3.16 (SD 2.77) at 8 and 32 weeks postoperative respectively (Fig. 1). There was a statistically significant difference over time as determined by one-way ANOVA (F[2.153]=5.340, p=0.006). A Hochberg's GT2 post hoc test revealed that the VAS was statistically significantly lower after 8 weeks (p=0.004) compared to baseline. There was no statistically significant difference between baseline and 32 weeks (p=0.201).

VAS – per treatment

Results of the repeated measures per treatment group are shown in Table 2 and Figure 1. All surgical interventions showed a decline in VAS over time at 8 weeks; nevertheless, there was only a significant decrease from baseline to 8 and 32 weeks after SMGE (F[2.34]=11.618, p<0.001). The VAS score after SMGE declined with 66% and 68% at 8 and 32 weeks respectively postoperatively compared to baseline. VAS decreased from a baseline value of 6.82 (SD 3.40) to 2.29 (SD 1.93) at 8 weeks and 2.17 (SD 2.58) at 32 weeks (Table 2).

Table 1. Patient demographics per patient and per treatment group.

	Patients, *n*=92	**BoNT-A, *n*=63**	**2DL, *n*=13**	**SMGE, *n*=16**
Age at intervention, mean (range), y:mo	9:7 (1–21)	8:2 (1–21)	11:8 (8–18)	13:5 (2–21)
Male:female ratio	47:45	32:31	7:6	8:8
Developmental age <4y	66 (72)	43 (68)	10 (77)	13 (81)
Main diagnosis				
CP	68 (74)	46 (73)	10 (77)	12 (75)
Other neurodevelopmental disability[a]	24 (26)	17 (27)	3 (23)	4 (25)
Degree of disability				
Ambulant or GMFCS level I–III	12 (13)	10 (16)	1 (8)	1 (6)
Non-ambulant or GMFCS level IV/V	80 (87)	53 (84)	12 (92)	15 (94)
Feeding				
Oral	32 (35)	29 (46)	0	3 (19)
Oral+gastrostomy	35 (38)	25 (40)	6 (46)	4 (25)
Gastrostomy	25 (27)	9 (14)	7 (53)	9 (56)
GERD	57 (62)	37 (60)	10 (77)	10 (63)

Data are *n* (%) unless otherwise stated. [a]Mainly based on a syndrome (Distal 18q, Sotos, Aicardi, Perisylvian, Da Silva, West) or metabolic (mitochondrial) disorder. BoNT-A, botulinum neurotoxin A; 2DL, submandibular duct ligation; SMGE, submandibular gland excision; CP, cerebral palsy; GMFCS, Gross Motor Function Classification System; GERD, gastroesophageal reflux disease (based on retrospective chart review).

Table 2. Absolute values on VAS at baseline and 8 and 32 weeks after surgery.

Intervention	**Baseline VAS (SD)**	**8 weeks**		**32 weeks**	
		VAS (SD)	***p*[a]**	**VAS (SD)**	***p*[b]**
BoNT-A, *n*=63	3.48 (2.47)	2.53 (2.71)	0.398	3.36 (2.71)	0.997
2DL, *n*=13	3.13 (3.98)	2.10 (2.13)	0.870	4.20 (3.39)	0.909
SMGE, *n*=16	6.82 (3.40)	2.29 (1.93)	**<0.001**	2.17 (2.58)	**<0.001**

Bold type indicates statistical significance. [a]Baseline to 8 weeks. Based on repeated measures one-way analysis of variance (ANOVA), Hochberg's GT2 post hoc test. [b]Baseline to 32 weeks. Based on repeated measures one-way ANOVA, Hochberg's GT2 post hoc test. VAS, visual analogue scale; BoNT-A, botulinum neurotoxin A; 2DL, submandibular duct ligation; SMGE, submandibular gland excision.

Secondary outcome

Recurrent LRTI – total group

After 32 weeks, the mentioned LRTI of the total group declined by 67% compared to the period before baseline (*n*=33 at baseline, *n*=11 at 32 weeks).

At baseline, 41% (33 out of 81 [11 missing variables]) suffered from signs related to LRTI in the year before treatment. After 8 and 32 weeks, only 11% (9/81) and 14% (11/81) of the caregivers mentioned any symptoms related to LRTI over the previous period. Overall Cochran's Q tests determined that there was a statistically significant difference in the proportion of patients with recurrent LRTI over time (χ^2[2]=26.600, p<0.001). Exact McNemar's tests determined that there was a statistically significant difference in the proportion of LRTI at 8 and 32 weeks compared to baseline (both p<0.001) (Figure 2).

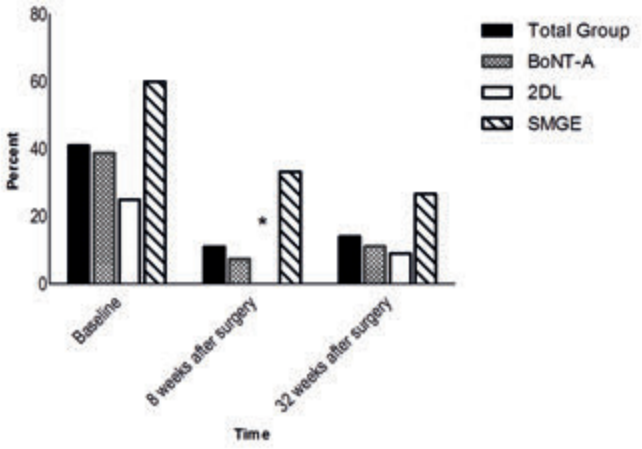

Figure 2. Proportion of overall lower respiratory tract infections. Total group: proportion of lower respiratory tract infections declined significantly based on McNemar's test at 8 and 32 weeks compared to baseline (Cochran's Q χ^2[2]=26.600, p<0.001). Botulinum neurotoxin A (BoNT-A): proportion of lower respiratory tract infections declined significantly based on McNemar's test at 8 and 32 weeks compared to baseline (Cochran's Q χ^2[2]=20.720, p<0.001). *No lower respiratory tract infections mentioned at 8 weeks for submandibular duct ligation (2DL). SMGE, submandibular gland excision.

Recurrent LRTI – per treatment

At baseline, SMGE had the highest number of patients with signs of LRTI (60%) compared to 25% (2DL) and 39% (BoNT-A). This was expected based on the selection criteria.

Analysis per treatment showed that only BoNT-A injections were significant over time (Cochran's Q χ^2[2] =20.720, p<0.001, McNemar's p<0.001 8 and 32wks), the proportions of LRTI were 7% and 11% at 8 and 32 weeks compared to 39% at baseline.

Correlation analysis

A point-biserial correlation was run to determine the relationship between VAS and LRTI at baseline. There was no significant correlation between both outcomes (r_{pb}=0.019, n=47, p=0.899).

Adverse events

There were no life-threatening complications. Complications directly linked to the intervention were reported for seven patients: three after BoNT-A injections because of thickened saliva, one after SMGE (postoperative rebleeding), and three in the 2DL treatment group (postoperative tongue infection, rebleeding, prolonged hospitalization).

DISCUSSION

This study revealed that even though BoNT-A, SMGE, and 2-DL relieved posterior drooling at 8 weeks and all treatments rendered a reduction in LRTI, only SMGE was significantly effective at both 8 and 32 weeks.

BoNT-A revealed the greatest decrease in LRTI at both 8 and 32 weeks after surgery (from 39% at baseline to 7% and 11% at respectively 8 and 32wks postoperative). This was in line with our expectations based on patient selection, in which younger patients with few complaints received the most conservative treatment option. On the other hand, BoNT-A is by nature a temporary agent that is only effective for a median of 22 weeks.[16] Correspondingly, there was an increase in VAS for posterior drooling from 8 to 32 weeks after BoNT-A.

We found no correlation between the reduction in VAS and LRTI. There are several explanations for the difference between VAS and LRTI. First, the VAS reflects only a short period of time. Second, there was a shorter time window for LRTI at 8 and 32 weeks compared to LRTI before baseline, causing a possible overestimation of the results. Third, VAS was obtained in a 'prospective' standardized manner whereas LRTIs were obtained based on caregivers' memory and medical record review, so LRTIs are subject to recall bias. Fourth, there are several other causes for LRTI besides posterior drooling.

According to our broad experience with the treatment of posterior drooling, SMGE showed a significant reduction in VAS. There is currently no criterion standard to evaluate posterior drooling. We conclude that a VAS for posterior drooling as judged by parents could serve as an appropriate outcome to address posterior drooling, whereas LRTI might not be as suitable in a retrospective setting. Future research should evaluate the relation between VAS for the severity of posterior drooling and LRTI in a prospective manner.

Baseline VAS was significantly higher for SMGE compared to BoNT-A and 2-DL. We assume differences between groups might be affected by the therapeutic sequence in which more severe cases and older patients were selected for surgical intervention. This is also reflected in the demographic data in Table 1 (e.g., gastrostomy feeding, intractable epilepsy, age). To be more specific, SMGE might show the largest effect because these are the patients that have more complex medical needs.

Previous studies with smaller sample sizes and different outcomes showed varying results. For example, Faria *et al.* revealed a significant reduction of antibiotic use and hospital stay days after treatment with BoNT-A injections in children with neurological impairment with drooling.[17] These results are in line with our findings.

Bilateral 2DL was temporarily effective for the treatment of posterior drooling, but there was a high degree of recurrence from 8 to 32 weeks. Although there is limited evidence for the effect of 2DL on posterior drooling, these results are in line with the previous literature that revealed some degree of recurrence in the medium to longterm.[15,18] Klem *et al.* reported absence of LRTI after ligation of the submandibular and parotid ducts,[19] suggesting a possible important role of the saliva flow from parotid glands in LRTI. The effect of SMGE differed among studies, [11,20,21] but the addition of parotid duct ligation offered promising results. The role of the parotid glands should therefore be investigated in future studies.

Considering the results of our study and the temporary nature of BoNT-A, SMGE offers a simple and rather effective alternative treatment for posterior drooling. As shown in previous studies and results in the current study, 2DL has a recurrence rate that we do not yet understand completely.[22,23] This is why the exact position of this surgical treatment needs to be investigated further before it is recommended as a first treatment option. If chosen for 2DL, recurrences could, in theory, still be treated with 'salvage' SMGE.

This is the first study to compare multiple invasive treatment options at different time intervals for the management of posterior drooling in a large population sample.

We are aware that clinical characteristics between the treatment groups differed, in which only the most severely impaired and older patients were mainly getting more invasive surgery, like SMGE. This could have influenced differences between groups; nevertheless, this reflects real clinical practice. After all, in clinical practice choice of therapy is based on patient characteristics and degree of symptoms. Another disadvantage of our study is the potential for recall bias.

Signs and symptoms of posterior drooling are sometimes non-specific and not always present,[24] which makes it difficult to investigate. Different studies have reported oropharyngeal aspiration in children with CP ranging from 27% to 38%; of these children 71% to 97% are silent aspirators without any of

the symptoms described above.[24–27] Over the years a variety of instrumental techniques have been used to detect aspiration (e.g., video fluoroscopic swallow studies, radionuclide salivagram, fiberoptic-endoscopic evaluation of swallowing). Unfortunately, clinical use in children with neurological impairment is sometimes difficult. Because of the absence of clear symptoms (e.g., silent aspiration) and diagnostic tools, posterior drooling results in a high burden of disease and impact on quality of life for patients and their caregivers. This could presumably be avoided by early recognition and associated preventive treatment.

This study should be interpreted as a 'first impression' on the value of treating the submandibular glands within the surgical treatment spectrum of posterior drooling. Future research in this field should aim to develop a diagnostic tool or measurement scale to identify patients suffering from posterior drooling and quantify/qualify outcomes. Moreover, a randomized clinical trial with a long-term follow- up would be useful.

CONCLUSION

Posterior drooling is a serious threat to the pulmonary condition of children with neurological impairment. This study showed that treating the submandibular gland is capable of reducing symptoms and LRTIs in these children. With the numbers we have it is difficult to draw solid conclusions, but it is likely that: (1) posterior drooling is an unfamiliar condition that needs attention and treatment; (2) reduction of 44% of the symptoms and 67% of the LRTIs seems possible; (3) a definite surgical intervention seems to be possible. In addition, surgery may be advisable, also at an earlier age, to prevent lung damage. SMGE is a simple treatment that showed the best and most permanent results on symptoms of posterior drooling.

Acknowledgements

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6

Chapter 7

Interventions for drooling in children and adolescents with neurodevelopmental disorders: how clinical practice and research evolved and mutually strengthened each other in our Saliva Control Team between 2000-2021

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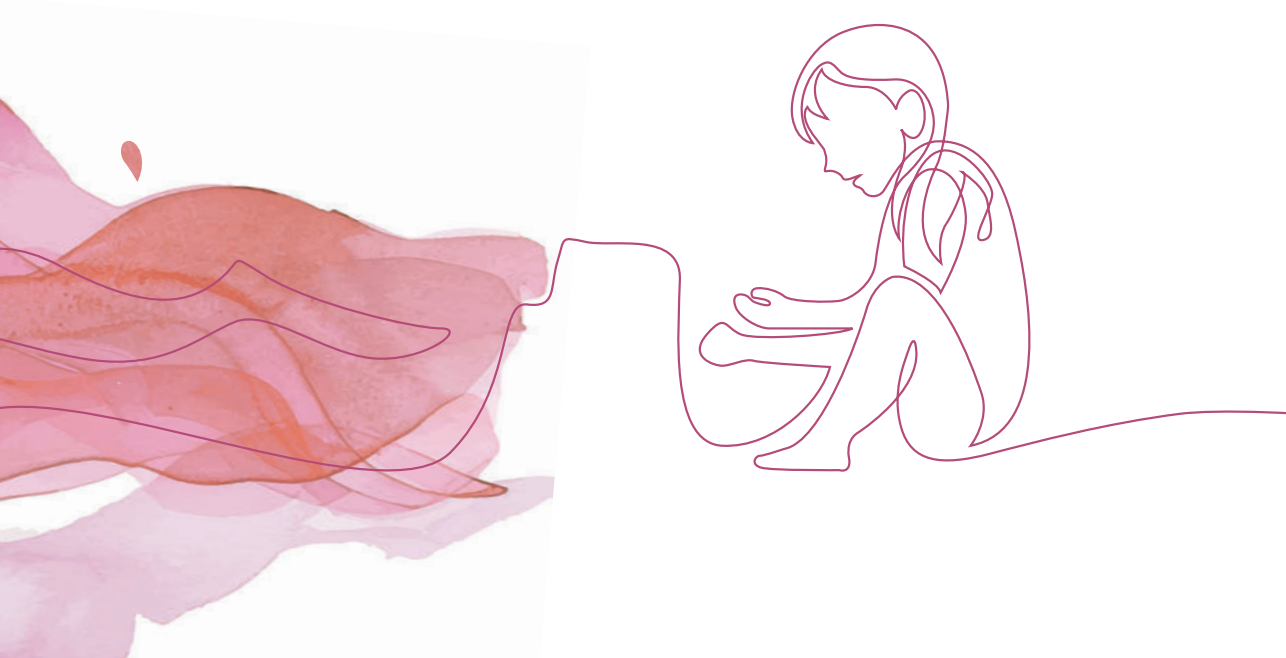


ABSTRACT

Drooling is a significant problem for children with neurodevelopmental disorders. Treatment consists of non-invasive interventions like self-management and anticholinergic drugs or more invasive interventions (i.e., botulinum neurotoxin injections or surgery). With this clinical overview, we aimed to describe how our clinical practice and research evolved and mutually strengthened each other in our Saliva Control Team over a 20-year period.

All patients referred and treated for drooling between 2000 and 2021 were included. We collected patient demographics and evaluated the treatment strategy of our team over the years.

Eight hundred and sixteen patients (515 males, 301 females) were included, totaling 1643 consultations. The average age of primary therapy was 9.5 years (SD 5.2). Four hundred and six (50%) of the patients were diagnosed with cerebral palsy, the majority (40%) with a GMFCS score V (transportation by wheelchair). Patients with a GMFCS level of V were more likely to undergo surgery. Over the years, we gained experience with both Botulinum Neurotoxin injections (n=970) and several surgical interventions (n=339). Over time, submandibular duct relocation with sublingual gland excision remains the first choice for persistent anterior drooling. For posterior drooling, submandibular gland excision is the preferred procedure.

INTRODUCTION

Drooling is generally considered abnormal after four years, except for a small preschool group (3-15%).[1] The estimated prevalence in children with cerebral palsy (CP) is reported as 40%, with the most severe and persistent drooling in the severest motor impairment (Gross Motor Function Classification System level IV and V).[2] Drooling results in physical, psychosocial, and emotional complications, in particular when untreated.[3]

Based on clinical assessment, drooling can be distinguished as anterior- and/or posterior drooling.[4] The main reason for drooling is a (sensori)motor impairment afflicting the oral phase (anterior drooling) or pharyngeal phase (posterior drooling) of swallowing, or both. Other contributing factors include, for example, a forward head and/or body posture, insufficient awareness of saliva, mouthing, and malocclusion.

Anterior drooling is the visible loss of saliva, which can cause perioral dermatitis, social problems like isolation and low self-esteem, and damage to furniture, electronic equipment, etc. Posterior drooling is defined as the spill and pooling of saliva from the oral cavity into the oro- and hypopharynx, with an impaired trigger to swallow, which may lead to distressing congested breathing, coughing etc., and at times saliva aspiration. The latter can lead to more severe complications related to aspiration, including recurrent lower respiratory tract infections and chronic lung damage.[5,6] The leading cause of this impairment in children or adolescents is CP.

Since treatment for drooling is complex, a multidisciplinary, coordinated approach is recommendable, as described before by Crysdale *et al*.[7,8] Parents or caregivers play a crucial role. We strive to bring together the caregiver's wishes (e.g., disease burden) and the team's expert opinion to enable shared decision-making.

The first step is to determine the cause, severity and consequences of saliva loss in the medical, oro-motor and social domains and to map the practical, social and emotional impact of drooling for the child and the family. After that, it can be decided if further management is warranted.[1] Analysis of problematic drooling starts with a comprehensive medical and oro-motor assessment with attention to underlying comorbidities (e.g., underlying medical diagnosis, refractory epilepsy, gastro-intestinal dysfunctions, induced drooling due to polypharmacy). In case self-management (an intervention aiming to increase the swallowing frequency or learn to wipe the mouth and chin) is considered a treatment, it is essential to assess the child's intrinsic motivation for treatment and the swallow- and self-management skills to control saliva loss.[9]

In a Cochrane review (2012), non-invasive treatments for sialorrhea are described and refer to oro-motor and oro-sensory therapies.[3] Self-management, oral appliances, and other options such as kinesio taping

and (mechanical or electrical) sensory stimulation or repeated muscle vibrations, as also pharmacological interventions (anticholinergic medications), might be non-invasive treatment options. More invasive treatment refers to botulinum neurotoxin injection into the salivary glands or surgical procedures which aim to redirect saliva by rerouting salivary flow, block the salivary flow of the glands through ligation or eliminate the production of saliva by excising the salivary glands.

Unfortunately, true consensus over a treatment strategy has never been reached.[3] Worldwide, there is experience in some specialized teams and research groups focusing on treating drooling (Australia, UK, USA, the Netherlands). We, the Dutch Saliva Control Team, developed and readjusted our approach based on our experiences and research over two decades. This clinical overview presents our expert opinion developed over the past 22 years, with the treatment of anterior and posterior drooling.

MATERIALS AND METHODS

Clinical evaluation

Our multidisciplinary saliva control team at the Radboudumc consists of a speech-language therapist (SLT), pediatric neurologist, rehabilitation specialist, psychologist and ENT specialist. When indicated, a pediatric consultant (e.g., dentist, paediatrician, dietician) is requested. In general, children from 3-4 years of age or above are accepted for evaluation at our outpatient clinic. At baseline, every patient is assessed by a speech-language therapist and pediatric neurologist, after which a consensus about the best treatment option is reached. The primary management consists of five choices: (1) no further treatment in our clinic other than advising SLTs, parents and referring specialists; (2) self-management; (3) pharmacotherapy; (4) botulinum neurotoxin type A (BoNT-A) injections or (5) surgery. No intervention or follow-up in our clinic is recommended when drooling is not considered pathological or if caregivers only need extensive advice from a multidisciplinary team. Follow-up depends on the choice of therapy; nevertheless, every patient in whom we start an intervention in our clinic is assessed by an SLT at 8- and 32 weeks after intervention. A stepwise approach to the clinical management of drooling at our Saliva Control Team is displayed in *the flowchart* attached, which we adapted from the AACPDM care pathway sialorrhea.[10]

Study population

We performed a retrospective chart review from January 1, 2000, to December 31, 2021. We used our database to collect data, which has also been the basis for previous reports by our multidisciplinary team. The study population consisted of all patients referred for drooling management and who gave informed consent. A total of 816 patients and 1643 consultations were identified. The number of patients assessed per year and the age of the patients at the time of initial assessment are depicted in *figure 1*.

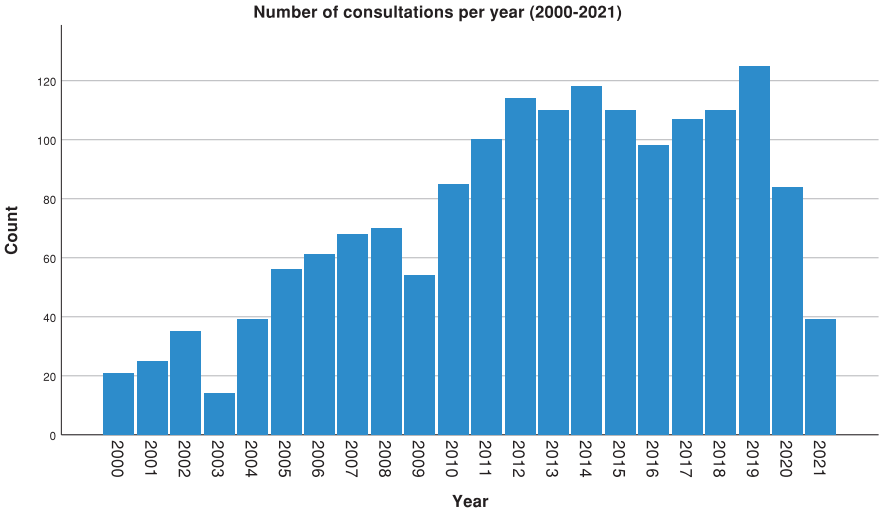


Figure 1a. Patients assessed each year. To the end of 2021, 1643 consultations have been assessed in the Saliva Control Clinic at the Radboud University Medical Center Nijmegen, the Netherlands. In 2020 and 2021 fewer patients have been assessed due to the COVID-19 pandemic.

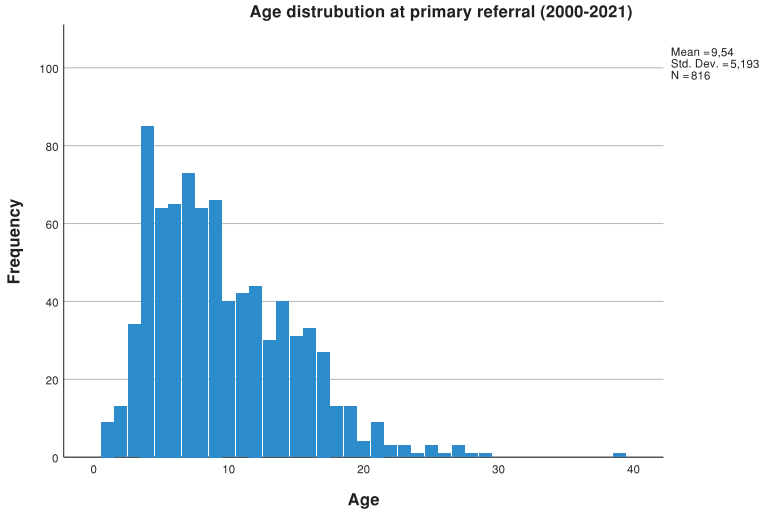
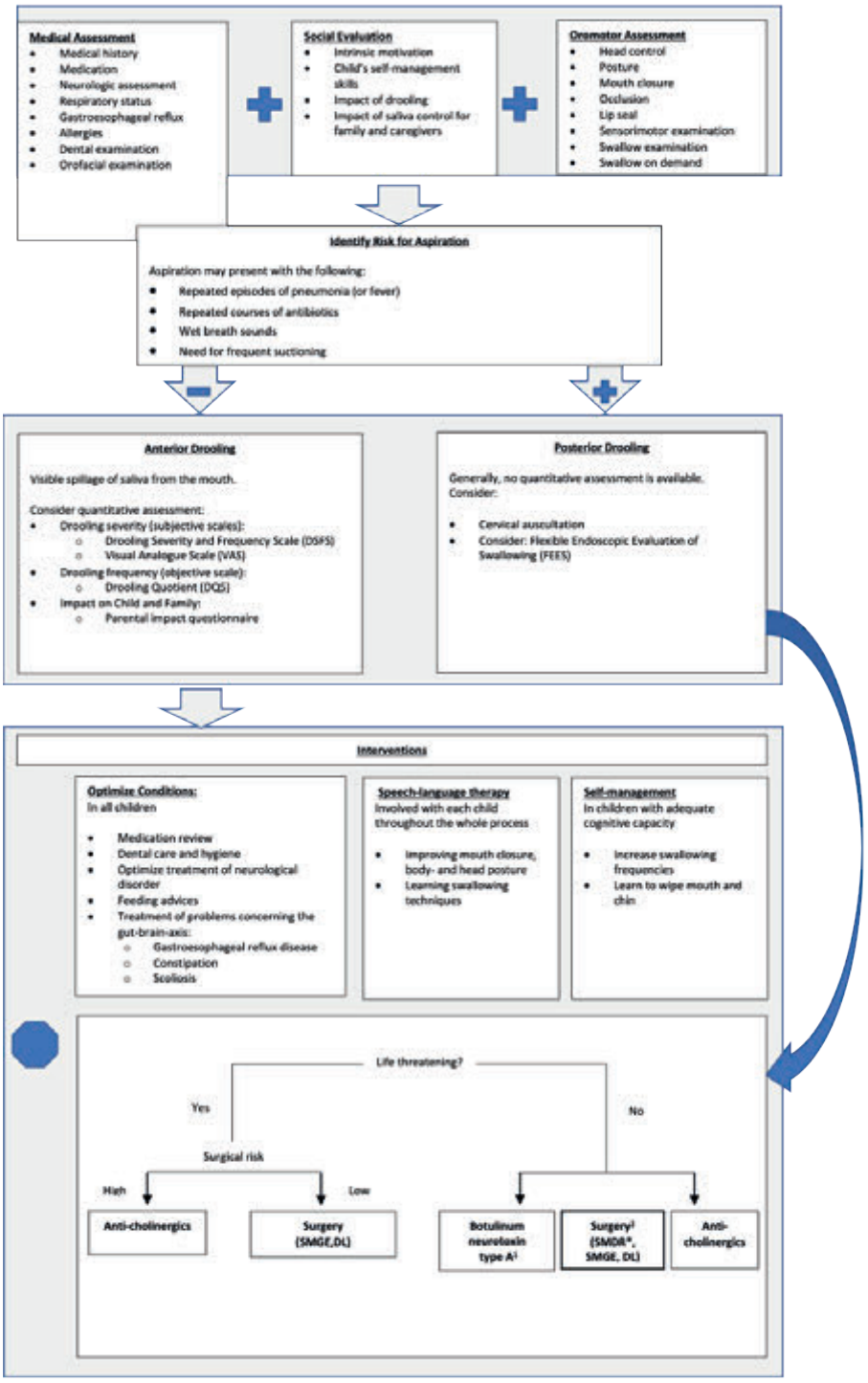


Figure 1b. The age of patients when first assessed. The average age of all patients assessed is slightly less than 10 years.


Medical Assessment
Medical history
Medication
Neurologic assessment
Respiratory status
Gastroesophageal reflux
Allergies
Dental examination
Orofacial examination
Social Evaluation
Intrinsic motivation
Child's self-management skills
Impact of drooling
Impact of saliva control for family and caregivers
Oromotor Assessment
Head control
Posture
Mouth closure
Occlusion
Lip seal
Sensorimotor examination
Swallow examination
Swallow on demand
Identify Risk for Aspiration
Aspiration may present with the following:
Repeated episodes of pneumonia (or fever)
Repeated courses of antibiotics
Wet breath sounds
Need for frequent suctioning
Anterior Drooling
Visible spillage of saliva from the mouth.
Consider quantitative assessment:
Drooling severity (subjective scales):
Drooling Severity and Frequency Scale (DSFS)
Visual Analogue Scale (VAS)
Drooling frequency (objective scale):
Drooling Quotient (DQS)
Impact on Child and Family:
Parental impact questionnaire
Posterior Drooling
Generally, no quantitative assessment is available.
Consider:
Cervical auscultation
Consider: Flexible Endoscopic Evaluation of Swallowing (FEES)
Interventions
Optimize Conditions:
In all children
Medication review
Dental care and hygiene
Optimize treatment of neurological disorder
Feeding advices
Treatment of problems concerning the gut-brain-axis:
Gastroesophageal reflux disease
Constipation
Scoliosis
Speech-language therapy
Involved with each child throughout the whole process
Improving mouth closure, body- and head posture
Learning swallowing techniques
Self-management
In children with adequate cognitive capacity
Increase swallowing frequencies
Learn to wipe mouth and chin
Life threatening?
Yes
No
Surgical risk
High
Low
Anti-cholinergics
Surgery (SMGE,DL)
Botulinum neurotoxin type A[1]
Surgery[1] (SMDA*, SMGE, DL)
Anti-cholinergics

Flowchart: Adapted from care pathway of the AACPDM, (CD, KvH, JvB co-authored the care pathway)

[1] Botulinum neurotoxin injection considered from 4 years of age.

[2] Surgery (submandibular gland excision (SMGE), submandibular duct relocation (SMDR), 1-4 salivary duct ligation (DL) considered from 12 years of age.

* Submandibular duct relocation is contraindicated if patients suffer from posterior (or combined antero-posterior) drooling or are at risk of developing it over the years due to a progressive swallowing disorder

Data collection

We collected demographics (age at intervention, gender, diagnosis (i.e., CP classified by GMFCS), and type of drooling). For every patient drooling was assessed by a trained SLT and pediatric neurologist at baseline and during follow-up visits in the outpatient clinic 8 and 32 weeks after treatment by the SLT. During baseline and follow-up, different outcome measurements were assessed. For anterior drooling, the Drooling Quotient (DQ5) [11] is the objective outcome, and a score on a visual analogue scale (VAS) combined with the Drooling Severity and Frequency scale and a parental impact questionnaire are the primary subjective outcome.[12] We continue to use the DQ5, VAS and a questionnaire on parental experiences when assessing aspects of drooling since there is only a weak correlation between the objective assessment of drooling and the subjective opinion of caregivers.[13]

Statistical analyses

We analyzed the characteristics of patients with SPSS version 27.0 for Windows (SPSS, INC., Chicago, IL, USA).

RESULTS

In this article, recommendations for saliva management have evolved into the following categories: no treatment given, self-management, anticholinergic medication, BoNT-A or surgery.

We included 816 patients in our study. All characteristics of the patients assessed during the 22 years from 2000 to 2021 are shown in *table 1*. Five hundred and fifteen (63%) patients were males, with a mean age of 9.5 years (5.2 SD) at primary management. Four hundred and six (49.8%) of the patients were diagnosed with CP, the majority (40%) with a GMFCS score of V (transportation by wheelchair). Slightly over two-thirds (67.7%) of the patients have an estimated developmental age below four years. Most patients (70.3%) were treated because of anterior or combined (27.8%) anterior and posterior drooling. Most patients suffered from profuse (72.5%) and continuous (56.7%) drooling based on the Drooling Severity and Frequency scale at baseline. Forty-four per cent (n=356) of the patients required additional therapy (BoNT-A, surgery or anticholinergic medication) after the initial intervention.

Table 1. Patient characteristics at primary referral (total) and per primary treatment strategy.

Characteristic	Self-management therapy	Glyco-pyrronium bromide	BoNT-A	Surgery	No treatment given in our clinic	Total
	N= 25 (3%)	N= 31 (4%)	N= 417 (51%)	N= 139 (17%)	N=204 (25%)	N= 816 (100%)
Gender, n (%) male	14 (56%)	24 (77%)	241 (58%)	91 (66%)	145 (71%)	515 (63%)
Age, y (SD)	10.6 (4.0)	8.7 (5.2)	8.6 (4.4)	14.7 (5.0)	8.0 (4.8)	9.5 (5.2)
Developmental age, n (%)						
<4 year	2 (8.0%)	21 (80.8%)	279 (68.0%)	88 (71.0%)	124 (71.3%)	514 (67.7%)
4-6 year, IQ<70	5 (20.0%)	0	54 (13.2%)	13 (10.5%)	17 (9.8%)	89 (11.7%)
4-6 year, IQ>70	0	2 (7.7%)	27 (6.6%)	0	11 (6.3%)	40 (5.3%)
>6 year	18 (72.0%)	3 (11.5%)	50 (12.2%)	23 (18.5%)	22 (12.6%)	116 (15.3%)
unknown	0	5	7	15	30	57
Cerebral palsy (n)	20 (80%)	12 (38.7%)	232 (66%)	78 (56%)	64 (31%)	406 (49.8%)
GMFCS						
I	3 (15.0%)	0	8 (3.5%)	2 (2.6%)	4 (6.7%)	17 (4.3%)
II	6 (30.0%)	0	32 (13.9%)	6 (7.8%)	7 (11.7%)	51 (12.8%)
III	6 (30.0%)	3 (25.0%)	46 (19.9%)	7 (9.1%)	11 (18.3%)	73 (18.3%)
IV	3 (15.0%)	2 (16.7%)	66 (28.6%)	20 (26.0%)	8 (13.3%)	99 (24.8%)
V	2 (10.0%)	7 (58.3%)	79 (34.2%)	42 (54.5%)	30 (50.0%)	160 (40.0%)
Drooling						
Anterior	23 (92.0%)	12 (42.9%)	301 (74.0%)	80 (62.0%)	136 (69.4%)	552 (70.3%)
Posterior	0	2 (7.1%)	3 (0.7%)	3 (2.3%)	7 (3.6%)	15 (1.9%)
Ant.-post.	2 (8.0%)	14 (50.0%)	103 (25.3%)	46 (35.7%)	53 (27.0%)	218 (27.8%)
Missing	-	3	10	10	8	31
Drooling severity						
Never drools	4 (21.1%)	3 (12.5%)	1 (0.3%)	6 (4.7%)	3 (1.7%)	17 (2.4%)
Mild	0	0	1 (0.3%)	0	2 (1.1%)	3 (0.4%)
Moderate	1 (5.3%)	1 (4.2%)	8 (2.2%)	2 (1.6%)	14 (8.0%)	26 (3.7%)
Severe	1 (5.3%)	8 (33.3%)	70 (19.5%)	25 (19.7%)	43 (24.7%)	147 (20.9%)
Profuse	13 (68.4%)	12 (50%)	279 (77.7%)	94 (74.0%)	112 (64.4%)	510 (72.5%)
Missing	6	7	58	12	30	113
Drooling frequency						
Never/Infreq.	4 (21.1%	3 (12.5%)	2 (0.6%	6 (4.7%)	6 (3.4%)	21 (3.0%)
Occasional	2 (10.5%)	4 (16.7%)	22 (6.1%)	4 (3.1%)	41 (23.3%)	73 (10.4%)
Frequent	5 (26.3%)	5 (20.8%)	108 (30.1%)	31 (24.4%)	62 (35.2%)	211 (29.9%)
Continuous	8 (42.15)	12 (50.0%)	227 (63.2%)	86 (67.7%)	67 (38.1%)	400 (56.7%)
Missing	6	7	58	12	28	111

Table 1. Continued

Required additional treatment	12 (48.0%)	9 (29.0%)	318 (76.3%)	17 (12.2%)	NA	356 (43.6%)

GMFCS (Gross Motor Function Classification Scale level descriptions; I: reduced speed, balance and coordination; II: limitations walking on uneven surfaces and inclines, and in crowds or confined spaced; III: walking indoors or outdoors on a level surface with assistance, wheelchair as needed; IV: reliance on wheelchair; V: no means of independent mobility.

The primary choice of treatment

The most commonly performed primary treatment for drooling included BoNT-A (n=417, 51%), in the majority into the submandibular glands (n=386), the second and third most performed is 'no treatment given' (n=204, 25%) and surgery (n=139, 17%), in particular, bilateral submandibular gland excision (SMGE) (n=61) and submandibular duct relocation with sublingual gland excision (SMDR) (n=52) (*figure 2)*.

Altogether, these patients had 1439 interventions, with a median of 2 treatments [minimum 1 – maximum 12] per patient. We recommended 'no treatment' in 204 patients, in which no 'direct' treatment was given. The role of each treatment will be outlined.

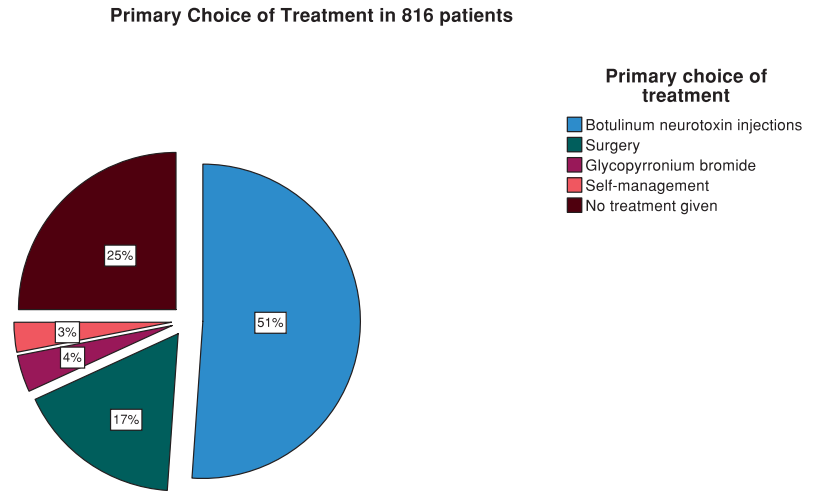


Figure 2a. Primary treatment for drooling between 2000 and 2021 in our Saliva Control Clinic (n=816).

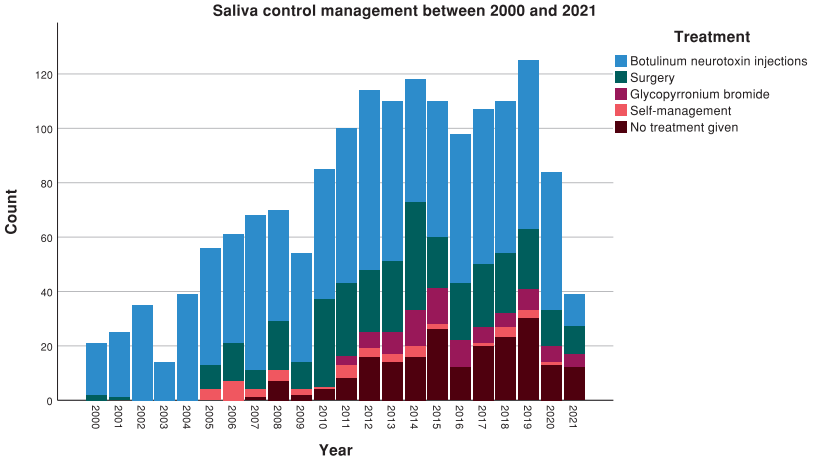


Figure 2b. Choice of treatment over the years in our Saliva Control Team (n=1643). The influence of the COVID-19 pandemic is visible in 2020 and 2021. Registration of glycopyrrolate for drooling (> age of 3) in a neurological condition in the Netherlands from 2019.

Non-invasive recommendations and interventions

No treatment: optimizing conditions

After extensive SLT and pediatric neurologist assessments, no immediate treatment in our clinic was indicated in 25% (204/816) of the patients assessed. No treatment was recommended in the child that was developing normally[1], when the drooling was of low priority or less severity (DQ<20%) and in the case, there was no saliva aspiration (posterior drooling). If possible, control of situational factors as previously described was advised.[4,14] Important situational factors are:

1. Oral motor issues: if necessary, the children were referred for speech-language therapy in the home region to practice the frequency and suction phase of swallowing.
2. Insufficient head and body posture; often a referral to the occupational therapist.
3. Dental conditions. Gingival inflammation will increase saliva production; referral to the dentist.
4. Review current medications (neuroleptics, seizure medication) that might influence drooling; refer to the treating neurologist.
5. Review of comorbidities, such as gastroesophageal reflux disease (GERD) and allergies; referral to the paediatrician.

Self-management

A self-management program can be valuable in children with adequate cognitive capacity (developmental age > six years), a motivated social support system and awareness of drooling as a problem. The intervention aims to increase the swallowing frequency or learn to wipe the mouth and chin and has proven to be effective in reducing anterior drooling. In 2005 we started this program, and over the years, 47 (3%) children were included at a reasonably stable level of under five treatments per year. At initial presentation, it was advised in 25 (3%) patients and performed in an inpatient setting in a child rehabilitation centre. In time, we adjusted this therapy to an outpatient setting. Nowadays, parents, therapists and/or teachers are applying for the self-management program at their own homes and schools, with support from the psychologist through remote (video) coaching and incidental outpatient visits. Demographically this group is characterized by a higher developmental age than all patients assessed, which goes hand-in-hand with the cognitive level needed for a successful intervention.[15]

Anticholinergic medication

Anticholinergic drugs reduce saliva production by inhibiting the neurotransmitter acetylcholine at the muscarinic receptors. Recently, the most used anticholinergic drug is glycopyrronium bromide, which has a response rate of 50%.[16] The disadvantages of this drug are the systemic side effects, like constipation, urine retention and flushing.[17] Nevertheless, glycopyrronium bromide has been gaining popularity over the past years since it was officially registered in the Netherlands for treating drooling in 2019. Because of the broad potential spectrum in which it can be effective, for example, as a temporary solution while waiting for a more permanent surgical intervention or as the child is expected to achieve saliva control during development. As shown in *figure 2b*, glycopyrronium bromide was first introduced in our clinic

in 2011. It is a requirement to pay attention to the side effects and educate parents extensively. A total of 31 patients started with glycopyrronium bromide as the primary intervention. Of these patients, 29% (n=9) needed additional therapy over the years. Fifty-two times glycopyrronium bromide was used in addition to the initial therapy. In our team, glycopyrronium bromide is widely applicable; in young and older patients and in anterior and posterior drooling cases.

Invasive interventions

Botulinum Neurotoxin Type-A injections into the salivary glands (BoNT-A)

Intraglandular BoNT-A is the most used treatment strategy in drooling in children from the age of four. Beside a significant decrease in salivary loss, this treatment has proven to improve quality of life as well [13,18,19]. Transient side effects have been described in 33%, including dry mouth, swallowing-, eating-, drinking-, and articulation difficulties. 19 As with treatment by anticholinergic drugs thickening of saliva should be considered. Also, the necessity of repeated anaesthesia is a disadvantage. In our clinic, ultrasound-guided BoNT-A injections administered under general anaesthesia are used as first-line treatment for patients in whom oral motor training has failed or, on the other hand, parallel to oral motor training as additional support, and other therapies are not considered feasible. Repeated injections are considered on a case-by-case basis. This approach has proven effective in approximately half of the patients for a median of 22 weeks.[18] However, since re-innervation almost always leads to recurrence and there is no evidence for a cumulative effect of repeated injections, botulinum toxin should be considered a temporary solution to relieve drooling.[18] This is also shown in *Table 1;* almost 77% required further (additional) interventions after primary therapy, significantly more compared to all the other groups. Nevertheless, like glycopyrronium bromide, BoNT-A is also widely applicable; it can be used in the very young (from 4 years of age), especially in case of profuse anterior drooling.

BoNT-A can be injected in the submandibular glands, parotid glands, or combined. Combined parotid and submandibular injections are generally reserved for patients with severe (antero)posterior drooling or for patients who did not sufficiently respond to exclusively submandibular injections. A total of n=970 (59%) BoNT-A injections have been given over the years; n=652 (40%) submandibular, n=285 (17%) combined and n=33 (2%) in the parotid glands. Submandibular gland BoNT-A was advised as a primary therapy for most patients (n=386, 47%). This makes sense because the submandibular glands produce the highest amount of saliva and are therefore targeted firstly.

Surgery

In case a more permanent treatment is needed, we offer a variety of salivary gland surgical procedures to be individualized for every patient and their needs (*figure 3)*. In anterior drooling, all surgical techniques can be used; but the most effective choice of therapy in our team is SMDR.[20, 21] However, this procedure is contraindicated in children who suffer from posterior drooling or progressive pharyngeal dysphagia. Research showed SMDR to be an effective treatment for drooling, in which most patients improve from frequent or constant drooling to occasional drooling. Children aged 12 years or older and those

with adequate head stability appeared to benefit the most from this technique. Side effects described included postoperative pain, secondary haemorrhage, prolonged intubation due to transient floor of the mouth swelling, fibrosis of the duct, eating difficulties, aspiration, and pneumonia.
If the patient suffers from posterior drooling or is at risk of developing it over the years due to a progressive swallowing disorder, SMGE or duct ligation (DL) is indicated. Both can be performed in anterior-, posterior, or combined drooling.[22,23]

Over the years, SMGE gained popularity, as shown in *figure 3*. This can be explained by our finding that it was almost (but not) as effective compared to SMDR.[24] But the most significant advantage of SMGE is the simplicity of the procedure and the fact that the postoperative hospital stay is shorter and patients do not need ICU surveillance. This is in contrast to SMDR, in which ICU surveillance is necessary because of the risk of swelling of the floor of the mouth and subsequent respiratory distress. The popularity of 2-DL shown in *figure 3* is assignable due to a recently published randomized controlled trial.[25] The simplicity of this procedure and the short-term effects are positive, but the increased recurrence rate needs further understanding and limits its applicability until then.

A total of 339 surgical procedures were performed between 2000 and 2021, as depicted in *figure 3*. Among the 816 patients, 17% (n=139) were treated surgically as the first treatment choice. However, 200 out of the 339 surgical interventions were given as salvage therapy because the primary therapy was insufficient. In general, surgical patients were significantly older than the other groups (mean age 14.7 (5.0 SD); preferably above 12 years of age, with some exceptions because of excessive drooling despite other strategies or in case of the risk of respiratory tract infections due to posterior drooling. Compared to self-management and BoNT-A, these patients had a higher GMFCS level.

The most crucial difference between surgical intervention and the other treatment strategies is the significantly lower amount of subsequent therapy after initial therapy. Only 12.2% (n=17) of patients had additional therapy. Bilateral parotid duct ligation seems the most reasonable reintervention after unsuccessful submandibular gland surgery.[26]

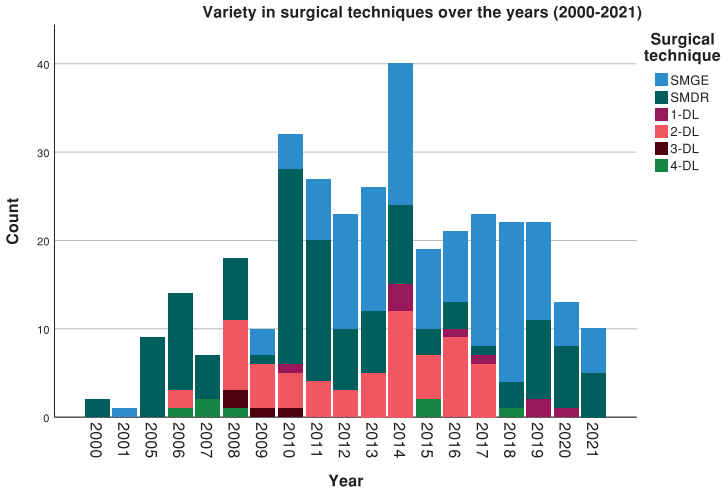


Figure 3. Variety in total number of surgical techniques (n=339) used by our Saliva Control Team over the years (submandibular gland excision (SMGE), submandibular duct relocation (SMDR), 1-4 salivary duct ligation (DL)).

Conclusion, practical considerations, and future perspectives

This clinical overview represents a large group of neurological impaired children that suffer from persistent drooling that have been treated for this matter between 2000 and 2021 in our saliva control team. Our Saliva Control Team allows a personalized approach. We combine the professional perspective of each individual in our multidisciplinary team, while the caregivers are the most essential and valued team members. Over the years, our treatment protocol has studied and adopted new therapies, which evolved from evidence-based practice to evidence-based medicine. Our multidisciplinary team evaluation with consensus decision-making has been proven successful within the treatment spectrum of drooling. This has resulted in a significant number of papers, a constant adjustment in our approach, and by now, the possibility of offering every child with a drooling problem individualized and personal care.

The leading cause of drooling is an inefficient swallowing process of a normal amount of saliva. Drooling is rarely, if ever, caused by hypersalivation alone.[27] Each intervention is based on examining the child's oral motor and cognitive functions through which we can offer targeted speech-language therapy or self-management. The diagnostic process is out of the scope of this article, and we focus on the interventions used. The next step in our treatment approach will be BoNT-A injections. Intraglandular injection of botulinum neurotoxin in the submandibular gland effectively denervates the salivary gland leading to a 70% reduction of saliva production from this gland.[13] This does not always lead to a clinically relevant or satisfying reduction of drooling. As a rule of thumb, we estimate that in 50% of the patients,

there will be a meaningful reduction of drooling for almost five months. [18] Repeated injections are necessary to maintain this effect. The necessity of, at least yearly, repeated injections under general anaesthesia limits the applicability to childhood until a disputable age of 10 to 14 years. In general, little progression of motor development is expected after this age, and a more definitive therapy should be advised if an intervention is requested.

Surgery is considered preferably beyond 12 years when conservative approaches, including botulinum neurotoxin injections, have failed or have undesirable side effects when drooling is so severe that conservative measures are unlikely to achieve a satisfactory outcome or compliance with conservative measures is challenging. There are multiple surgical techniques used to manage drooling, in which the preferred technique depends on the institute and experience of the surgeon. Our most common and currently used techniques are SMDR, 1-4 DL or SMGE. [21,24,25]

In the case of anterior drooling in a child with a non-progressive neurological disorder who has been (safely) orally fed over the years, SMDR is the preferable surgical intervention unless contra-indicated. Although SMGE reduces the saliva production of this gland to zero, SMDR has an even more significant effect.[21] The release of submandibular saliva in the oropharynx, where the relocated duct ends, seems responsible for this. It triggers a swallowing action. Many parents mentioned having noticed this effect postoperatively. The pharyngeal phase of swallowing should be intact and expected to be maintained in the future if a submandibular duct rerouting is considered. If a child has been fed orally, if there is a non-progressive impairment and aspiration or related pneumoniae, have not or only occasionally occurred until the age of the child at that time (>12 years of age), the pharyngeal phase of swallowing can be considered sufficient enough to perform this procedure. Suppose, in time, this situation would change unexpectedly, and posterior drooling or progressive aspiration of saliva would still occur. In that case, one could still perform a submandibular gland excision as an escape surgery.[6]

Posterior drooling has only recently been described, and the importance of this condition needs clarification. The majority of children we treat for posterior drooling suffer from CP. The leading cause of early death in children with CP is related to respiratory causes. Pneumonia, often related to aspiration, is the main cause. Posterior drooling is underestimated as an important contributing factor.[6]

In the case of posterior drooling, with or without anterior drooling, SMDR is contra-indicated. A reduction of saliva is necessary. Submandibular gland excision with or without clipping the parotid duct is an effective procedure. It is difficult to say when parotid duct ligation needs to be added to the procedure. In cases of life-threatening aspiration, it is advisable to do so; in milder cases we consider reducing saliva step by step to prevent xerostomia. If insufficient, parotid duct ligation can still be added. As a general rule we try to preserve at least one parotid duct if there is still oral feeding. [6,22,26]

SMGE is an effective, relatively simple surgical procedure to reduce submandibular saliva production in both anterior and posterior drooling. SMGE is a procedure that most ENT- and maxillofacial surgeons are trained to perform. It causes a significant reduction of saliva in the majority of patients. Over the past 20 years, we investigated the different surgical techniques' positions for treating both anterior and posterior drooling. Nowadays, SMGE is a first-choice procedure in posterior drooling patients for whom intra-oral surgery is considered a problem and can be an alternative for SMDR in anterior drooling as outlined above. Complications are in general rare and mild, and since it is an extra-oral procedure, it seems to have fewer postoperative problems (i.e., feeding, dental care).[6,23]

One to four duct ligation (1- 4 DL) or clipping of the submandibular and/or parotid ducts is a simple and effective treatment to rapidly reduce salivary flow.[25,28] Salivary glands swelling postoperatively is seen in general but resides within a week in the majority of cases. Over the years, we witnessed that the risk of recurrence of salivary flow, possibly by alternative pathway formation, and complications, such as ranula formation are larger than with a SMGE. Therefore, we reserve this procedure for situations in which other surgical procedures are not feasible for whatever reason (often a procedure in palliative situations). This reluctance is reflected in *figure 3*. We still investigate ways to improve the results of salivary gland clipping.

Recently, it has been propagated to start an earlier surgical treatment, instead of BoNT-A, by Formeister et al.[29] The authors concluded that surgical interventions were more effective for drooling. In line with the recent study of Weitzman et al[33] we concluded that our team is more conservative, especially in patients with the isolated hindrance of anterior drooling, and postpone surgery to an older age if saliva control is expected to improve due to the child's development. We do decide to operate earlier if the children suffer from posterior drooling with loss of quality of life (*flowchart)*.

Although the effectiveness of glycopyrronium bromide has been demonstrated in three randomized, controlled trials[30], the positioning of the treatment in relation to other used interventions needs to be clarified. This is currently a research topic in our team, and the results will be expected in the near future.

Our Saliva Control Team is a consistent team of professionals dedicated to developing a stepwise, personalized treatment approach. Over the years, we made various adjustments to our approach based on published research and with a focus on personalized medicine. For example, *van Hulst et al.* developed the Drooling Infants and Preschoolers Scale (DRIPS) in 2018.[1] The DRIPS made it possible to validly compare and visualize the development of saliva control in an individual infant or preschooler and allows referring clinicians to initiate individually targeted interventions if children outperform timely. Another example is the awareness of the importance of situational factors, as described above. Although, to date, we cannot predict failure or success, we emphasized more and more on the importance of these individual situational factors. This is reflected in the rise of 'no treatment given' over the years in *figure 2b*. Also, our surgical way of thinking has been adopted over the years, reflected in *figure 3*. While we hypothesized that the relatively simple submandibular gland excision could replace the

more complex submandibular duct relocation in case of anterior drooling, we know nowadays that submandibular duct relocation is still the procedure of first choice in a selection of patients based on individual characteristics. The same lesson we learned for two-duct ligation, which hypothetically would be an easier to perform, intra-oral and quicker alternative procedure compared to submandibular gland excision. However, the high long-term recurrence rate made us doubt about the exact position of this procedure, which is the reason for ongoing research about salivary duct clipping.

Over the years, we have had numerous national and international visitors to our clinic and shared our knowledge worldwide via congresses, workshops, and webinars. By presenting this clinical overview and evidence-based practice, we further share our knowledge and try to highlight this still underestimated and often undertreated problem. The lack of an international consensus on the treatment of drooling emphasizes the importance of exchanging this knowledge between medical professionals, patients, and parents/caregivers.

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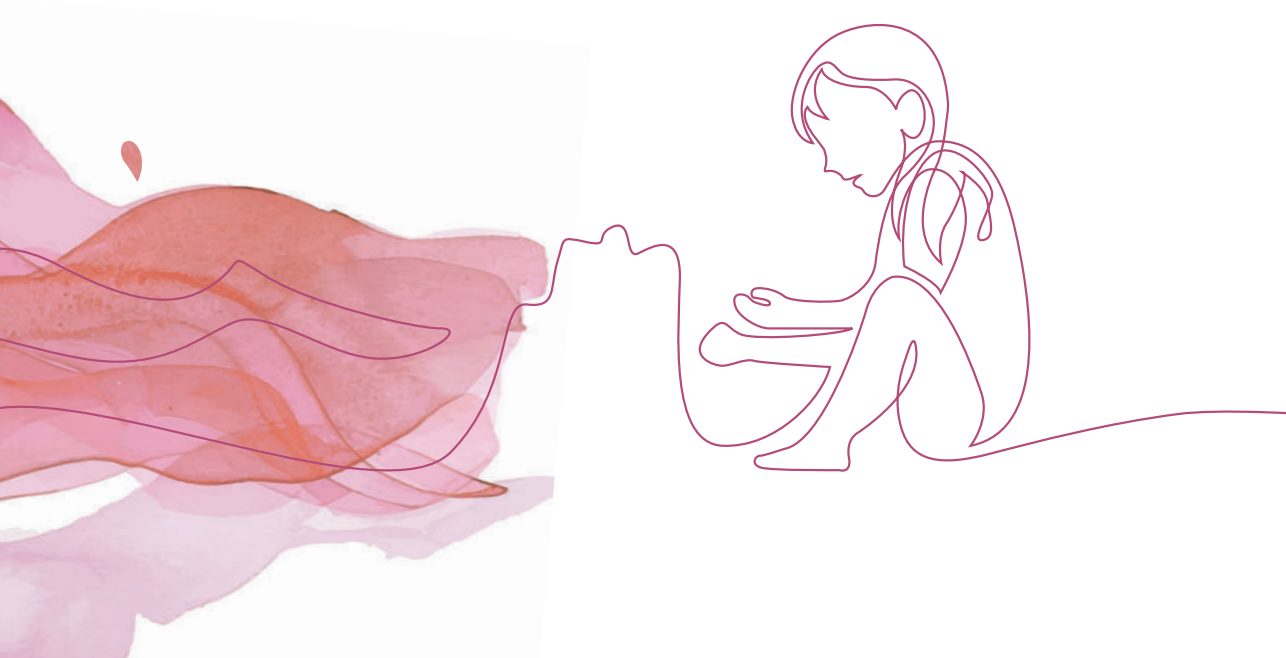
SUMMARY AND GENERAL DISCUSSION



SUMMARY

We have six major salivary glands and numerous accessory salivary glands as outlined in the introduction. As the submandibular glands are generally believed to contribute most to daily saliva production it seems logical to aim at these glands when considering treatment options for drooling. Submandibular saliva can be reduced by blocking its innervation with botulinum toxin injections, rerouting (SMDR) or clipping of Wharton's duct (2-DL) or resecting the gland (bilaterally (SMGE)) as a whole. However, drooling is caused by multiple factors and with all these surgical interventions we only aim at reducing, rerouting, or eliminating submandibular saliva production. That is why submandibular gland surgery in theory, is proposed as the most reasonable permanent solution in case of persistent and severe drooling. Beyond the age of approximately ten to twelve years we do not expect major advancement in the development of oral motor skills anymore. Also, in general, most of the secondary teeth have erupted beyond this age, which temporarily influences the severity of drooling. From that age on we prefer a more permanent surgical solution to treat drooling. Whether or not reducing, rerouting, or eliminating saliva production will lead to a satisfying reduction of anterior (visible) and/or posterior drooling (saliva aspiration; respiratory tract infections) is still a difficult question to be answered and success will partly depend on all the other contributing factors.

We delineated the current state of therapies given for drooling and identified the gaps which are the rationale for this thesis. With a focus on clinical applicability, the aim of the first chapters is the evaluation of various clinical outcomes of the surgical submandibular glands approaches for severe anterior drooling. The second part of this thesis reviews our clinical practice since the origin of our Saliva Control Team in the year 2000. We highlight the importance of recognizing and treating posterior drooling and describe the lessons learned by our team over a more than 20-year period.

Chapter 1

The aim of chapter 1 was to evaluate the objective and subjective results after SMGE on anterior drooling. A historical cohort of 26 patients (mean age 15.6 years) was analyzed at baseline and during standardized follow-up measurements at 8- and 32-weeks post-intervention. The main outcomes included a (subjective) VAS (range 0-100), the Thomas-Stonell and Greenberg Classification for drooling severity and frequency and the (objective) Drooling Quotient (DQ, range 0-100%). Clinical response was another important outcome of this study. This was defined as ≥ 50% reduction of the (objective) DQ and/or the reduction of 2 standard deviations of the (subjective) VAS. We found a significant reduction in drooling based on the drooling quotient (DQ). The DQ declined from 33.5 at baseline to 17.1 at 8 weeks, and 9.9 at 32 weeks. Additionally, a significant decrease was found for VAS. The VAS decreased from 75 at baseline, to 34.7 at 8 weeks and 40.5 at 32 weeks. A clinical response rate of 63% 32-weeks post-intervention was established. In this first chapter, we concluded that SMGE is an effective therapy for

drooling in children and adolescent with neurodevelopmental disabilities. This procedure is a valuable and an effective solution for drooling when SMDR is contraindicated.

Chapter 2

In the second chapter we aimed to investigate the long-term effect after SMGE in a historical cohort of 61 patients with non-progressive neurodevelopmental disabilities. The main outcome of this study was the long-term subjective effect on VAS and the Thomas-Stonell and Greenberg classification. Caregivers' satisfaction and adverse event with the procedure were among the secondary outcomes. The follow-up time was 313 weeks (median) [range 123-502 weeks] and 35 caregivers (57%) responded on the long-term follow-up questionnaire. Overall, we found a significant improvement for both subjective scores compared to baseline. VAS improvement diminished slightly in time but remained significant with a large effect size (mean difference -21.8, $t(26) = 4.636$, $p < 0.0005$, Cohen's D 0.89). Submandibular gland excision also elicits a statistically significant change on both drooling severity and frequency ($Z = -4.361$, $p < 0.0001$ for drooling severity, $Z = -3.065$, $p = 0.002$ for drooling frequency). Nevertheless, some recurrence of drooling on both subjective measures occurred, and 17% needed additional therapy for drooling. Still, 66% of the caregivers and/or patients would recommend SMGE to peers. We concluded in this study that a relatively simple to perform surgical procedure like SMGE largely remains effective in the long term with a small risk of bothersome recurrence.

Chapter 3

In all surgical procedures external visible scarring can be a matter of concern especially in the cervico-facial region. Chapter 3 describes our experience with SMGE for the treatment of drooling, with special attention to the external bilateral transcervical scars. Since the standard alternative techniques (SMDR or 2-DL) for anterior drooling are transoral, we studied the parents' opinion on the mature external scars in relation to treatment outcome. We used a validated questionnaire (the Patient and Observer Scar Assessment Scale) to evaluate observer and clinician satisfaction. After exclusion, 26 patients were studied, 25 responded to our questionnaire, of these caregivers 96% considered the scars acceptable. Seventy-six percent of the patients and/or caregivers (19/25) were satisfied with the overall outcome. Notably, we found no correlation between satisfaction and the appearance of scars. Success was, as hypothesized, correlated with a decrease in drooling severity ($p=0.035$) and the amount of respiratory tract infections ($p=0.042$) in the case of prominent posterior drooling. We conclude that the appearance of scars after SMGE does not influence satisfaction, but the treatment outcome does.

Chapter 4

The minimally invasive alternative to submandibular gland excision is submandibular duct ligation (2-DL). Chapter 4 describes the results of a randomized, interventional, controlled, and partly single-blinded study. This study compares submandibular botulinum toxin injections with 2-DL to treat excessive anterior drooling. The primary outcome included treatment success (≥50% reduction in DQ or VAS after 32 weeks). Fifty-three patients were included in the intention-to-treat analyses. Submandibular

duct ligation showed a significantly higher response to treatment after 32 weeks on both the subjective (VAS) as well as the objective outcome (DQ). Treatment success after 8 weeks was 88.9% for 2-DL and 53.8% for botulinum toxin injections. This success declined to 63% after 32 weeks for 2-DL, vs. 27% for botulinum toxin injections. The total number of adverse events (AE) and postoperative complaints were higher for 2-DL (AE in 41%) than for botulinum toxin injections (AE in 19%). Overall, we concluded that 2-DL (submandibular) is a more effective treatment for drooling than botulinum toxin but with a higher risk of adverse events and postoperative complaints. Moreover, there is an unexplained certain degree of relapse between 8 and 32 weeks after 2-DL.

Chapter 5

This chapter focused on the effect of revision surgery for anterior drooling refractory to submandibular duct surgery. We aimed to find an explanation for unsuccessful surgery on the submandibular duct and in particular to reveal if treatment failure is due to surgical failure or whether other clinical variables could explain recurrence. We described 11 interventions in 10 patients and investigated the effect of reintervention on drooling. A reference cohort was used to control for clinical variables. Eight patients underwent duct ligation as an initial intervention for drooling and two patients SMDR. In 7 cases, SMGE was chosen as a subsequent reintervention, expecting surgical failure to cause persistent drooling. In the other 3 cases, the parotid glands were expected to be the source of refractory symptoms, and parotid duct ligation was subsequently performed. Only three patients were successful after reintervention, defined as a 50% reduction of VAS and/or DQ from baseline to 32 weeks. No difference was found between the technique of reintervention (parotid duct ligation or SMGE). Compared to the reference cohort there were significant more cases with severe dental malocclusion (50% vs. 21%, p=0.047) and severe speech disorders (80% vs. 42%, p=0.042). Still, most likely, recurrence of drooling after submandibular duct surgery is not caused by surgical failure of the primary intervention because completely removing the submandibular glands did not improve success rates. Dental malocclusion and speech disorders might negatively influence treatment outcomes. However, additional studies are needed on the topic of non-responders after interventions for anterior drooling, with particular attention to the parotid glands as an alternative source of refractory drooling.

Chapter 6

Posterior drooling and aspiration of saliva is more and more recognized to be a serious threat to the pulmonary condition of children with a neurological impairment. We propose a more aggressive reduction of saliva by some sort of invasive treatment of the submandibular gland. The aim of this chapter was to evaluate the effect of submandibular gland surgery (resection vs 2-duct ligation vs submandibular gland botulinisation) in case of severe posterior drooling. We identified a retrospective cohort of 92 children treated between 2000 and 2016 by our Saliva Control Team. Mean age at time of surgery was 9 years (range 1-21y). The main outcome included a specific (subjective) Visual Analogue Scale ($VAS_{posteriordrooling}$;0-10) for signs and symptoms of posterior drooling at baseline and 8-weeks and 32-weeks follow-up. As a secondary outcome we assessed the reduction in occurrence of lower

respiratory tract infections at follow-up. We solely included patients who have undergone invasive or surgical treatment of the submandibular gland (botulinum toxin injections (n=63), SMGE (n=16), or 2-DL (n=13)). A significant reduction in $VAS_{posteriordrooling}$ over time was observed in the total group of 92 patients. Based on sub-analyses, we found a significant effect after SMGE at 8 weeks and 32 weeks follow-up, from 6.82 (SD 3.40) at baseline to 2.29 (SD 1.93) after 8 weeks and 2.17 (SD 2.58) after 32 weeks). The $VAS_{posteriordrooling}$ after botulinum toxin injections and 2-DL significantly decreased at 8 weeks follow-up, but not at 32 weeks. This study showed that treating the submandibular gland can reduce symptoms and LRTIs in posterior drooling. Submandibular gland excision showed better and more permanent results on symptoms of posterior drooling than botulinum toxin injections or bilateral submandibular duct ligation. For posterior drooling, we recommend submandibular gland resection as the surgical procedure of preference.

Chapter 7

In the final chapter we present the efforts and experiences of our Saliva Control Team in the treatment of drooling over 20 years, since the origin of the team. We present the challenges of treating drooling, the lessons we learned during the years and our most recent tailor-made approach. Over time we performed 1643 consultations and treated 816 patients. We started with the treatment of botulinum neurotoxin injections in the submandibular glands in 2000 and over the years gained experience with a variety of surgical techniques. We learned that a more permanent surgical solution is preferable from the age of 10-12 years. Over the years, SMGE gained popularity, which can be explained by our finding that it was almost (but not) as effective compared to SMDR, the simplicity of the procedure and the fact that the postoperative hospital stay is shorter and patients do not need ICU surveillance. Another reason for the increasing popularity of SMGE is its' position in the treatment of posterior drooling. Over the years, we recognized more and more that posterior drooling is an underestimated but serious physical threat to the pulmonary condition of these patients that needs to be treated and submandibular gland excision is the first-choice procedure. The less invasive 1 to 4-duct ligation has a place in the treatment of both anterior and posterior drooling, however due to recurrence the exact position has yet to be defined. In this chapter, we also emphasize on the importance of evolving research into clinical practice and on the important role of the caregivers in our multidisciplinary team. Moreover, we present a comprehensive overview of all the challenges in managing drooling and conclude that 1) we have evaluated several invasive treatment options that are more or less effective in different situations, 2) we are becoming more and more aware of how to offer every child or adolescent with drooling the best-personalized care, 3) our teams' evaluation and decision making are essential to that.

GENERAL DISCUSSION

In this thesis, we generally have focused on the value of bilateral submandibular gland excision (SMGE) as a treatment option for both anterior as well as posterior drooling. We evaluated whether SMGE can serve as a salvage procedure in case clipping (2-DL), or rerouting (SMDR) failed and we emphasized the importance of SMGE in the treatment of posterior drooling. Finally, we presented this surgical procedure in a historical perspective of our saliva control team which has been active over 20 years now.

Submandibular gland surgery for anterior drooling

The position of submandibular gland excision

We can conclude that SMGE is the procedure of first choice in case of:

1) Severe anterior drooling in children with progressive pharyngeal swallowing disorders beyond the age of 10-12 year.
2) If submandibular duct relocation (SMDR) is contra-indicated. For example, in case of a contra-indication for postoperative invasive airway ventilation.
3) Posterior drooling (discussed later).

The visible spill of saliva (anterior drooling) has been the focus of research for years, however a personalized treatment approach has still to be defined. Unlike SMDR or 2-DL, SMGE has been a well-known procedure for decades. It has been described for the first time in literature from the 1950s through the 1970s, related to submandibular gland tumors. The notoriety of this procedure made us speculate that submandibular gland excision could be the first-choice procedure in drooling surgery, instead of SMDR. We have been able to demonstrate the significant objective and subjective decrease of drooling at 8 and 32 weeks postoperatively following SMGE. We showed a clinical response rate of 63% well past 32 weeks follow-up. Which means that although we can treat two-thirds of all the patients with success, there are non-respondents or patients who recur even after complete removal of the submandibular glands.

Recurrence of drooling and long-term effects

If we compare the most notable outcomes of drooling surgery (Drooling Quotient (DQ) and drooling on a Visual Analogue Scale (VAS)) no matter the type of approach, it is striking that after 32 weeks follow-up there is a visible trend: a diminished effect. This suggests recurrence of drooling in the long term, despite the surgical approach, as it is visible after SMGE, SMDR and 2-DL.

The reason for recurrence of drooling is still an unexplained phenomenon. As there is no evidence of surgical failure, alternative salivary pathways were proposed as the most important reason for failure after 2-DL. However, based on chapter 5, in which we presented the limited effect of salvage SMGE after 2-DL in a group of non-respondents, we can carefully reject this argument. Furthermore, we speculated between surgical failure (SMGE as salvage therapy) or the underrated role of the parotid glands (parotid

duct ligation) if response fails. Although we can only remain speculative due to the quality of the study design, we found that bilateral parotid duct ligation, instead of SMGE, was the most effective subsequential therapy after initial surgery on the submandibular ducts. This might indicate that surgical failure was not the case. Hence, we carefully concluded that there is no position for salvage SMGE.

Compensatory hypersalivation from the parotid glands could be a reason for treatment failure of SMGE, especially since it has been shown that submandibular botulinum neurotoxin injections can lead to a compensatory increase in parotid flow.[65] In our team, there is little experience with the surgical treatment of the parotid glands, because of the risk of xerostomia. On the other hand, there is a lot of experience with the treatment of botulinum neurotoxin injections in the parotid glands without obvious xerostomia through appropriate patient selection. Most often, the parotid glands are treated with botulinum neurotoxin in a stepwise approach, in which the submandibular glands are targeted first. It can be argued that we are too conservative in treating the parotid gland surgically. In the future, the role of surgery on the parotid glands, as a similar two step approach compared to botulinum neurotoxin injections, or even as a first choice 'sandwich therapy', should be further investigated since this could be a reason for recurrence or non-respondents. The risk of thickened saliva and subsequent aggravation of swallowing and chewing problems after treating the parotid glands should always be kept in mind.

The role of postoperative hypersalivation by the sublingual- or even accessory glands after submandibular gland surgery is also debatable. In current practice, the sublingual glands are not considered a therapeutic target. We believe these glands are only responsible for approximately 10% of saliva produced. However, the role of the sublingual gland in the etiology of recurrence cannot be completely ruled out. Since SMDR is the only procedure that involves surgery on the sublingual glands, and the effect of SMDR with excision of the sublingual glands is still superior compared to SMGE.

Another, more general reason for recurrence of drooling is that children with cerebral palsy are 'growing into a deficit', indicating an expected degree of recurrence.[66] This principle describes the fact that children with cerebral palsy suffer from ongoing physical deterioration over the years. With for example posture deterioration and a subsequent need for muscle relaxants, which can lead to a diminished therapy effect on the long term. A stepwise approach, in which the parotid glands are targeted at a later age when the child grows into a deficit, is a potential promising personalized way of treating these children. However, before evolving our treatment protocol, the surgical treatment of the parotid gland definitely needs more attention in future research. For many years, it is speculated that recurrence of drooling is due to, yet unidentified, clinical variables. In our study, there were significant more patients with severe dental malocclusion and serious speech disorders who required reintervention compared to a reference cohort, still this is not a sufficient explanation for recurrence.

All things considered, it is presumable that recurrence of drooling after salivary gland surgery is multifactorial and, unfortunately, difficult to predict. Even when the proportion of saliva production by

the submandibular gland is zero (after SMGE), this still not guarantees a clinically significant response. With a success rate of 63% 32-weeks after SGME, there is still a significant population with a disappointing result. In daily practice, it is not the successes but failures that make people think and reconsider. In this matter, the high rate of response failure raises more questions to be answered and is a focus for future research.

Submandibular gland excision in comparison to the alternatives

As mentioned before, alternative surgical procedures for SMGE are 1) transoral submandibular duct relocation with sublingual gland excision (SMDR) and 2) submandibular duct ligation (2-DL).

We hypothesized that SMGE would be the simpler alternative to the therapy of first choice: SMDR. The latter has, in our hospital, the downside of an extensive postoperative care in the ICU department with at least one night of invasive airway ventilation, because of the risk of swelling of floor of the mouth.[71] Moreover, we noticed that several patients could not be treated with SMDR, because of a pharyngeal swallowing disorders or we anticipated on the risk of posterior drooling in the future. These patients could benefit from eliminating saliva instead of rerouting it. In general, SMDR is advised in patients with safe swallowing, adequate posture, and non-progressive neurological disease. Hence, it is advised in the 'neurologically better' patients who drools.

The most important disadvantage of SMDR in comparison to SMGE is that the procedure is difficult to perform, while SMGE can be performed in the hands of most surgeons because of its' simplicity and the fact that most surgeons are familiar with this procedure. Because SMDR is performed in a neurologically 'better' patient (i.e., degree of functioning (disability, type of swallowing disorder etc.)) it is difficult to make a direct comparison between the two interventions. However, based on comparable research performed by our saliva control team, we can conclude that in anterior drooling the effectiveness of SMDR is slightly superior compared to SMGE.[48] Although, SMGE reduces saliva release to zero, SMDR has an even larger effect due to the relocation of saliva into the oropharynx where it triggers a swallowing action.

In April 2012, we started a RCT to compare two-duct ligation (or submandibular duct ligation (2-DL)) with botulinum neurotoxin injections in the submandibular gland. We hypothesized that this procedure could be the less-invasive alternative for SMGE in the same category of patients. Submandibular duct ligation is a relatively short procedure compared to SMGE, with a slightly lower risk of surgical adverse events (4% vs 8%). The trial revealed promising results on anterior drooling after 2-DL, however with a still to be explained, degree of recurrence. The latter being the reason of the uncertain position of this procedure in comparison to SMGE. More certain, since we found that the effectiveness of SMGE is superior compared to 2-DL, especially in the long term.

In SMGE, the gland is resected as a whole including disrupting its innervation, while in 2-DL the parasympatic innervation is left unexposed. It has been reported that the parasympatic nerve remains a reservoir of progenitor cells for salivary organogenesis or tubulogenesis.[67] This underlines the hypothesis of recurrence due to alternative pathway regeneration after 2-DL, which could explain the differences in

the long term in comparison to SMGE. Patients needed additional therapy in 17% after submandibular gland excision, compared to 33% after 2-DL in the study of Bekkers *et al.,* also suggesting that the effect after submandibular gland excision might be more long-lasting.

Submandibular gland excision is the only extraoral approach, compared to the other two intraoral approaches mentioned above. Many parents mentioned this as the main disadvantage of submandibular gland excision when we discussed the different treatment options. The external visibility of the scar, especially in the cervical region, even made some parents doubt about this procedure. In many, this contrasts with the child's self-perception. That is why we studied the influence of the external scars as described in chapter 3. We found that almost all caregivers considered the scars acceptable, and it did not influence satisfaction with the procedure. Hypothetical, an extraoral approach can even be beneficial to the outcome, since postoperative healing after an intraoral approach could lead to more saliva stimulation and a negative change in oromotor mouth behavior in children with cerebral palsy. To minimize external scarring, endoscopic submandibular gland surgery is a potential alternative approach. Major disadvantages of this, not yet adapted, approach are the associated learning curve and costs that go with this technique. The results of chapter 3 can be considered during the informed consent when the team leaves the choice between submandibular duct relocation and bilateral submandibular gland excision to the caregivers to decide.

In a nutshell, we can conclude and advise that SMGE is indicated in case of anterior drooling, in which SMDR is contraindicated or not advisable because of, for example, a progressive neurodevelopmental disability. Alternatively, to SMGE, caregivers could opt for 2-DL; a less extensive procedure, which can be considered especially when prolonged anesthesia is contraindicated, however with a higher risk of recurrence in the long-term. In specific cases of anterior drooling, caregivers can also opt for the more extensive SMDR, with a smaller chance of recurrence, but with a longer hospital admission.

Salivary gland surgery for posterior drooling: The importance of submandibular gland excision

Posterior drooling has previously been described, as a condition in which leakage of saliva to the oropharynx occurs, leading to pooling, choking incidents and (silent) aspiration.[9] The importance of this condition needs clarification, but most important seems to be underestimated. Even though swallowing disorders are commonly described in children with cerebral palsy, the prevalence of posterior drooling is still unknown. We identified 92 out of 475 patients with any degree of posterior drooling, indicating a prevalence of almost 20% in children with neurodevelopmental disabilities who drool. In children with cerebral palsy the main cause of early death, over 50%, is related to chronic respiratory problems, often related to aspiration of saliva or gastric contents.[11]

Over the many years we noticed a lot of patients with recurrent respiratory tract infections in need for ongoing antibiotics, that could benefit from a significant reduction of saliva. Unfortunately, in comparison to all the other health related problems these patients must deal with, posterior drooling seems to be

an underestimated problem. In addition, we noticed that parents and professionals are often not aware of the mechanism and existence of saliva aspiration, in contrast to the more visible anterior drooling. We highlighted this important matter, that has a major influence on general health and quality of life of these impaired children and adolescents. Children with recurrent lower respiratory tract infections have a tremendous burden of disease with frequent extended hospital admissions, intensive care unit admission, oxygen support at home etc. Not to mention, the enormous effect salivary gland surgery can have on quality of life and burden of care when palliative care is indicated.

To prevent aspiration, children are often fed by gastro- or jejunostomy. To further minimize aspiration, gastroesophageal reflux and other patients characteristic (e.g. posture, bowel obstruction, allergies) needs to be assessed and treated.[68] If despite different conservative intervention, signs and symptoms of posterior drooling still occur, subsequent more invasive treatment of this condition is required. We presented the promising results of submandibular gland surgery for posterior drooling and identified that SMGE is the procedure of first choice for posterior drooling. In severe posterior drooling or in case of recurrence, parotid duct ligation in combination with SMGE or in a stepwise approach can be considered. From our experience, it is difficult to decide when parotid duct ligation needs to be added to SMGE in a single-step procedure. As a rule, we try to preserve at least one parotid duct if there is still oral feeding. Moreover, thanks to previous research conducted by our team, we do know that botulinum neurotoxin is not advisable in case of posterior drooling, because of the risk of thickened saliva. This can cause subsequent swallowing and chewing disorders, and the risk of pooling of saliva with an even higher risk of aspiration to occur.[69]

In conclusion, posterior drooling is a challenging condition for the clinician and researcher, that needs to be addressed. Submandibular gland excision offers promising results, with a low risk of xerostomia. However, in posterior drooling there are still multiple challenges left. The main challenge, not yet discussed, is the lack of a standard criterion to diagnose and evaluate posterior drooling, nor is there a classification of hindrance despite a visual analog scale. Over the years a variety of instrumental techniques have been used to detect aspiration (e.g., video fluoroscopic swallow studies, salivagram, fiberoptic-endoscopic evaluation), however standardized clinical use in children with neurodevelopmental disabilities is difficult. In patients with signs of saliva aspiration without obvious drooling, endoscopic and radiographic assessments, should be completed before offering drooling procedures. We used a subjective outcome measure in our study, obviously a more objective outcome is highly desirable.[72] The second major challenge is that signs and symptoms of posterior drooling are sometimes non-specific and not always present. For this reason, posterior drooling is a so-called 'silent killer' as a result of the pulmonary sequela.[11] Having said this, we can assume that there are many patients in whom posterior drooling is not even recognized as a potentially 'easy' to treat condition. Moreover, the prevalence in our study might be a serious underestimation. From this perspective, we believe there are still a lot of gaps to be filled, and more important a lot of profit to be made because of the high morbidity and mortality rates associated with (saliva) aspiration in cerebral palsy.

Challenges and lessons learned

This is the first thesis that thoroughly highlights the effectiveness and the position of SMGE for the treatment of both anterior- and posterior drooling in children with neurodevelopmental disabilities. We described the experiences of a saliva control team that has been active over more than 20 years. A team that distinguishes itself with consistency, dedication and ongoing research with clinical evolvement, which made us one of the leading Saliva Control Teams worldwide. The numerous amounts of research performed by our team, led to a continuous adjustment of our purposed tailor-made medicine. This stands for an individual, stepwise, and personalized approach.

We faced various challenges which are partly inherent to drooling. First, our patient population is very heterogeneous, and so is all the literature regarding the child who drools. With the goal of an international consensus for the drooling child, we must consider this challenge when we are comparing outcomes. Second, drooling impacts not only the patient (with an enormous variance in self-perception), but also the caregivers and their environment which makes it difficult to measure the correct burden of disease. Nevertheless, our definition of success, which includes both an objective and subjective outcome measure, has proven to be related to the impact of drooling on daily life, social interaction, and self-esteem. We strongly recommend our colleagues, to use our combined definition of success. Finally, most of the research was performed in a non-randomized matter, within a small cohort. However, with over 20 years of experience, this is still the largest cohort published so far. At last, research in the field of posterior drooling is challenged by the obscurity with the phenomenon.

Over the years our team has gone through a learning curve while constantly adjusting our approach and way of thinking. When we started this thesis we were primarily interested in the objective and subjective outcome variables and evaluated treatment response by using our own definition of success. However, the definition of success kept on changing, reflecting clinical insight. In time, we also noticed the inconsistency of our criterium in clinical practice and the inability to compare our results with other global research groups, which makes the use of a composed success criterion challenging. However, we cannot emphasize enough that parents are the most essential team members in our multidisciplinary team with a perfect expert opinion of their child's needs. The value of a subjective outcome measure in addition to an objective outcome measure is therefor, in our opinion, almost essential. On the other hand, if we reduce drooling (objective) but the child still drools, and caregivers are not satisfied (subjective), this will not be reflected in our composed definition of success. This challenge has already been described by our team in 2020.[37]

This 'response disparity' underlines the importance of tailored medicine, in which every patient has his own disease burden, wishes and expectations and thus individual definition of success. To state, this also marks a critical aspect of this thesis: the difficulty of measuring the burden of disease for the individual patient. In other words, are we treating the child or the caregivers? Changes in the impact of drooling may be valued differently depending on the social and cultural situation. Despite a personalized treatment approach, we also suggest a personalized approach for the evaluation of drooling. For this

purpose, a new outcome measure based on the Canadian Occupational Performance Measure (COPM) has been developed and used by our team.[70] The use of this outcome measure underlines the role of the parents as a valuable team member. The position of this new outcome measure called SCM (Saliva Control Measure) is still subject of current research.

During the years, various healthcare professionals have been involved while treating the child with drooling: general practitioners, speech-language pathologists, rehabilitation specialists, neurologists, pediatricians, ear-nose-and-throat surgeons, dentists, and most important, all the caregivers and patients. In chapter 7, we shared the experience we have gained and the lessons we have learned during two decades of collaboration. It is important to emphasize the value of a solid, dedicated, multidisciplinary team in a tailor-made approach. In time, we pragmatically evolved research and clinical practice, based on over 50 peer reviewed publications by our team. Our goal is to evaluate the effectiveness of interventions in real-life routine practice and try to bridge the gap between science and clinical practice. In our opinion, a 'bottom-up' approach is still considered the most applicable and reasonable. A flowchart of how we treat the drooling child is presented in chapter 7. We start with the least invasive therapy, adapt this to the patient, and then move up the ladder. Referral to a multidisciplinary team, or at least a speech language therapist with experience in drooling is crucial. Especially, since it is important to distinguish between pure anterior drooling, or the presence of signs and symptoms of posterior drooling which needs to be assessed in a different way.

Concluding remarks and future perspectives

A firm hypothesis about the role of submandibular gland surgery for the treatment of drooling inspired us to write this thesis. We aimed to describe the role of submandibular gland surgery, starring bilateral submandibular gland excision, within the challenging treatment of drooling. This thesis demonstrated that bilateral submandibular gland excision is an effective and safe treatment for anterior and posterior drooling.

In the concluding remarks, we would like to emphasize one of the main findings of this thesis, but also the subject that needs further thorough evaluation: the efficacy of submandibular gland surgery in case of posterior drooling. We described our first experience in treating this condition with 3 different interventions. The long-term effect of saliva aspiration should not be underestimated, since subsequent chronic lung damage has a significant impact on morbidity, mortality, and quality of life in children with cerebral palsy. As stated, half of these children is said to die from pulmonary causes of which the majority is related to aspiration problems. Early identification and treatment that lowers the risk of pulmonary deterioration are therefore important to consider, as also stated in a consensus statement about prevention and management of respiratory disease in young people with CP.[73] However, early identification of signs and symptoms related to posterior drooling is extremely difficult. Our team already did some pioneering work and developed the 'Pediatric Posterior Drooling Scale,' in which speech-language therapists can use cervical auscultation as a

diagnostic tool and evaluate the effect of treatment. Until now, the scale still needs to be validated. Treating salivary aspiration and obstruction incidents in severely handicapped children must also be considered as a necessary palliative care. Research on this important matter should focus on therapeutic interventions, for example the efficacy of anticholinergic medication, the long-term effects of surgical interventions and sandwich therapies.

A second recommendation for future perspectives is about the still not well understood high rate of recurrence of anterior drooling, as mentioned throughout this thesis. As stated in the different chapters, we are still unable to predict response to treatment and, more specific we cannot explain why there is such a huge amount of recurrence, or less likely surgical failures. Even when we completely rule out the production of submandibular saliva, there is still a considerable risk of recurrence. Theoretically, it is most reasonable to expect that the parotid glands have a significant role in this matter. In children with severe brain injury, salivary gland innervation might be remodulated, causing a different distribution in the amount of saliva produced by the major salivary glands (more parotid or sublingual gland stimulations). The role of the parotid and sublingual glands should still be of interest in future research. Even more, the development of a treatment protocol for non-respondents after surgical interventions would be highly relevant to offer every child with drooling a uniform, but still personalized and stepwise approach.

As an ending remark, we would like to state the importance of sharing knowledge about children with drooling, even when there is a low grade of evidence. This thesis is an example of mostly clinical, pragmatical research. We highly encourage evidence-based medicine, in which study topics are investigated with the highest priority for daily practice in the best possible study design. However, when research is scarce, the importance of sharing clinical knowledge with other medical professionals and caregivers is essential to change perspectives and reach consensus. Especially, since international consensus on how to treat drooling is missing.[34] From this perspective, the unrevealing of the physiology of drooling is needed, for example, to give insight into why some children drool and some do not and why some children respond to treatment, and some do not. In a niche where RCTs are scarce, it takes courage to support a personalized approach from an expert- instead of an evidence-based point of view. This thesis adds a small piece in the puzzle of treating the child who drools.

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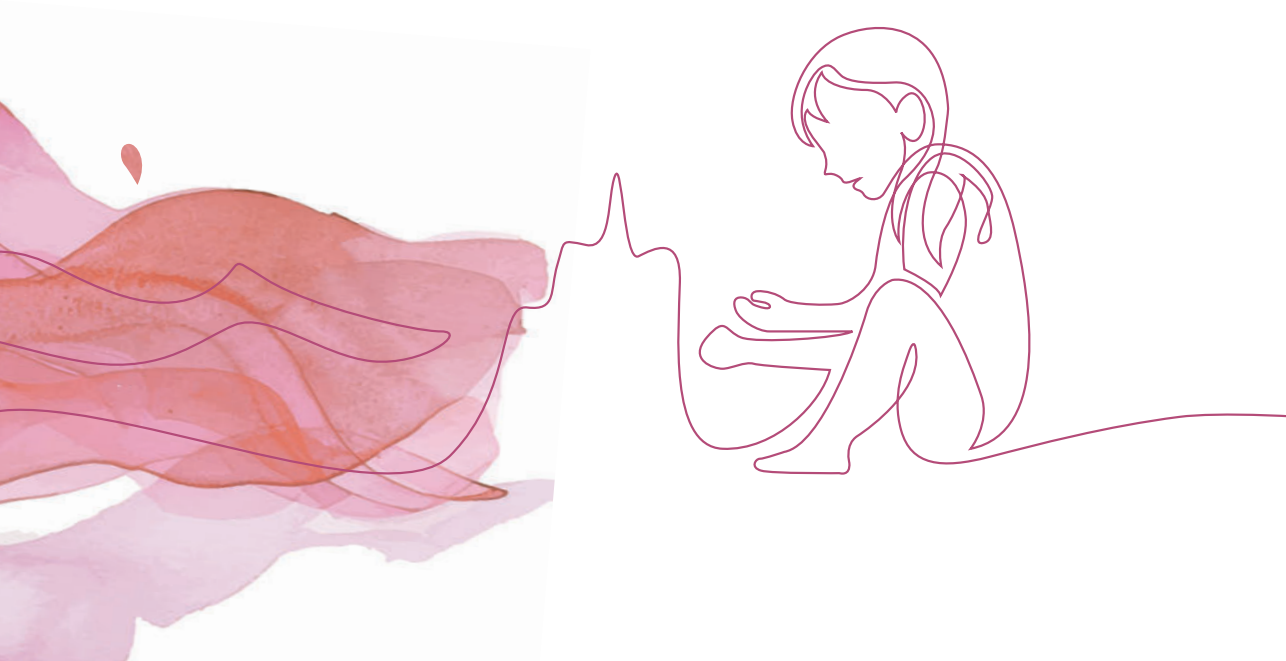
International collaboration: working towards an international consensus statement for drooling



AACPDM SIALORRHEA CARE PATHWAY

Bottom Line 'Evidence-Informed' Recommendations for Children/Youth with Cerebral Palsy who have Sialorrhea

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https://www.aacpdm.org/publications/care-pathways/sialorrhea-in-cerebral-palsy

Definition

Sialorrhea refers to drooling of saliva as a result of limitations in a person's ability to control and swallow oral secretions. Anterior drooling is defined as saliva spilled from the mouth that is clearly visible. *Posterior drooling* occurs when saliva spills through the oropharynx and into the hypopharynx. In children and youth with cerebral palsy (CP), sialorrhea is usually the result of limited oromotor control as a result of muscle incoordination and sensory perception difficulties rather than excessive salivation.

Impact: Why is sialorrhea important?

Sialorrhea occurs in approximately 40% of children/youth with CP and can have significant medical and psychosocial impact.

Medical concerns:

- Posterior pooling can have the serious consequence of chronic aspiration resulting in recurrent infections and progressive lung disease.
- Presence of saliva on the chin leads to frequent wiping, causing skin irritation and breakdown.

Psychosocial concerns:

- Anterior drooling of saliva may result in the need for frequent clothing changes, may damage books, computers, toys and other equipment, and spray from the mouth while talking.
- Social embarrassment experienced by children/youth, their caretakers and siblings can be considerable and may lead to isolation and low self-esteem.

Target Population: Children/youth between the ages of birth and 25 years with CP who drool

Target Clinical Providers: Physicians, therapists, psychologists and nurses treating children/youth with CP who drool

Assessment

Discussion with providers from multiple disciplines is recommended

- Medical assessment
  - Emphasis on medications, history of aspiration, respiratory status and lower airway examination, neurologic assessment (craniofacial control, posture, impact of medicines, epilepsy, developmental age equivalent), gastroesophageal reflux disease (GERD), presence of allergy, orofacial examination (dentition, oral hygiene, upper airway), hydration.
- Social evaluation
  - Intrinsic motivation and child's self-management skills, impact of sialorrhea and importance of saliva control to family
- Motor/Oromotor assessment
  - Head control, positioning, mouth closure, occlusion, lip seal, sensorimotor evaluation, swallow on demand, ability to wipe own saliva
- Drooling can be assessed quantitatively with a variety of tools for severity and frequency as well as impact on the child and family [Drooling Quotient, Teacher Drooling Scale, Drooling Severity and Frequency Scale, Visual Analogue Scale (VAS), Drooling Impact Scale (DIS), number of bibs, frequency of clothing changes]. Quantification can aid in gauging response to interventions.
- Differentiation between anterior and posterior drooling is important. They may appear independently or may coexist. Most often, clinical information such as repeated episodes of pneumonia, repeated antibiotic courses for respiratory reasons, evidence of chronic inflammatory lung disease, and significant need for suctioning are used as indicators of posterior drooling. Additional investigations to consider include salivagram and fiberoptic endoscopic evaluation of swallowing; however, they may not be necessary or appropriate.

Treatment options

A number of treatment strategies are available although there is no clear consensus as to which are safe and effective. Goals of treatment target: 1) improvement of oromotor control of secretions; 2) enhancement of a child's ability to behaviorally manage secretions; and 3) reduction of saliva production or rerouting of salivary flow. When possible, a multidisciplinary team approach is recommended, progressing from conservative to more invasive treatments until saliva control is improved and side effects, if present, are manageable. Complete control is often not possible. Additionally, surgical intervention may not be curative. All of the strategies that follow may be appropriate for anterior drooling; oromotor and orosensory strategies, behavioral strategies, and oromotor appliances are not recommended for posterior drooling. Duct relocation is contraindicated for posterior drooling.

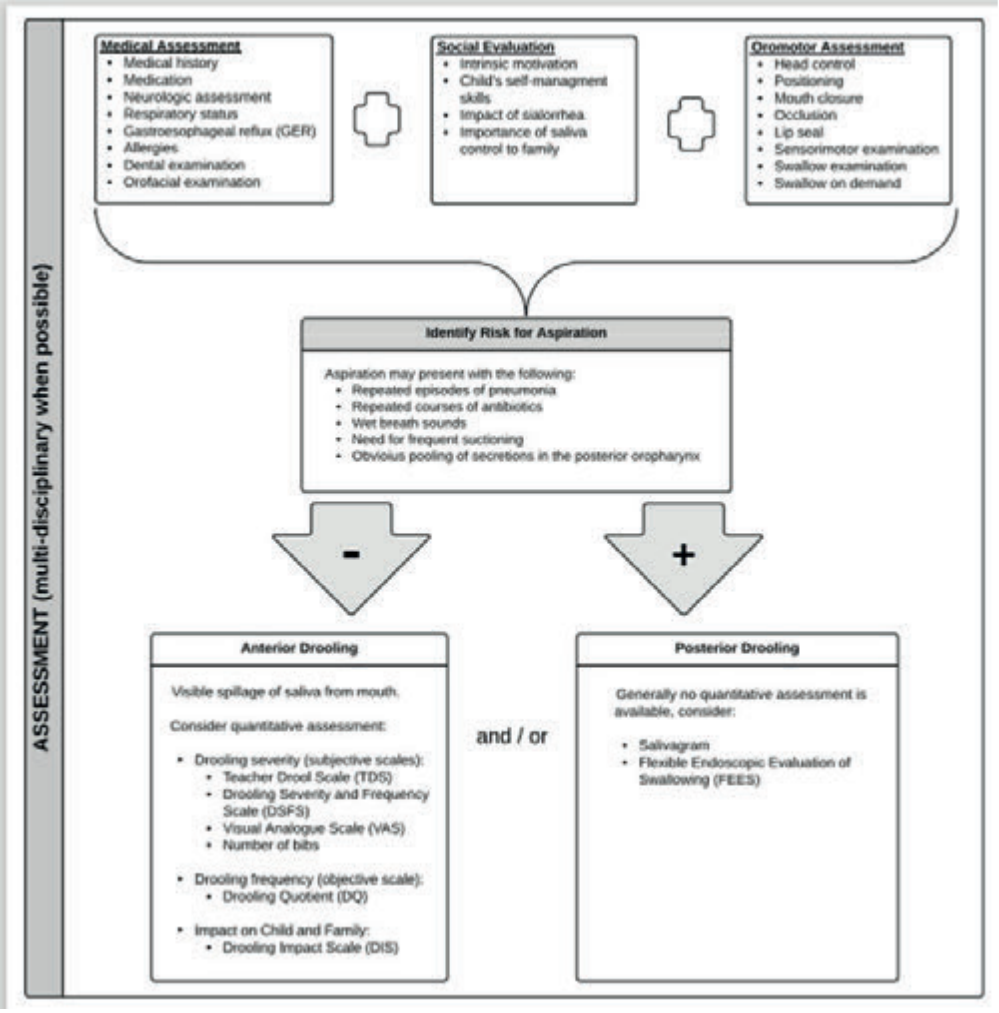
- Optimize conditions
  - Optimize positioning and medical management of factors that affect drooling. Consider whether medications being used for other conditions, such as epilepsy, are increasing drooling.

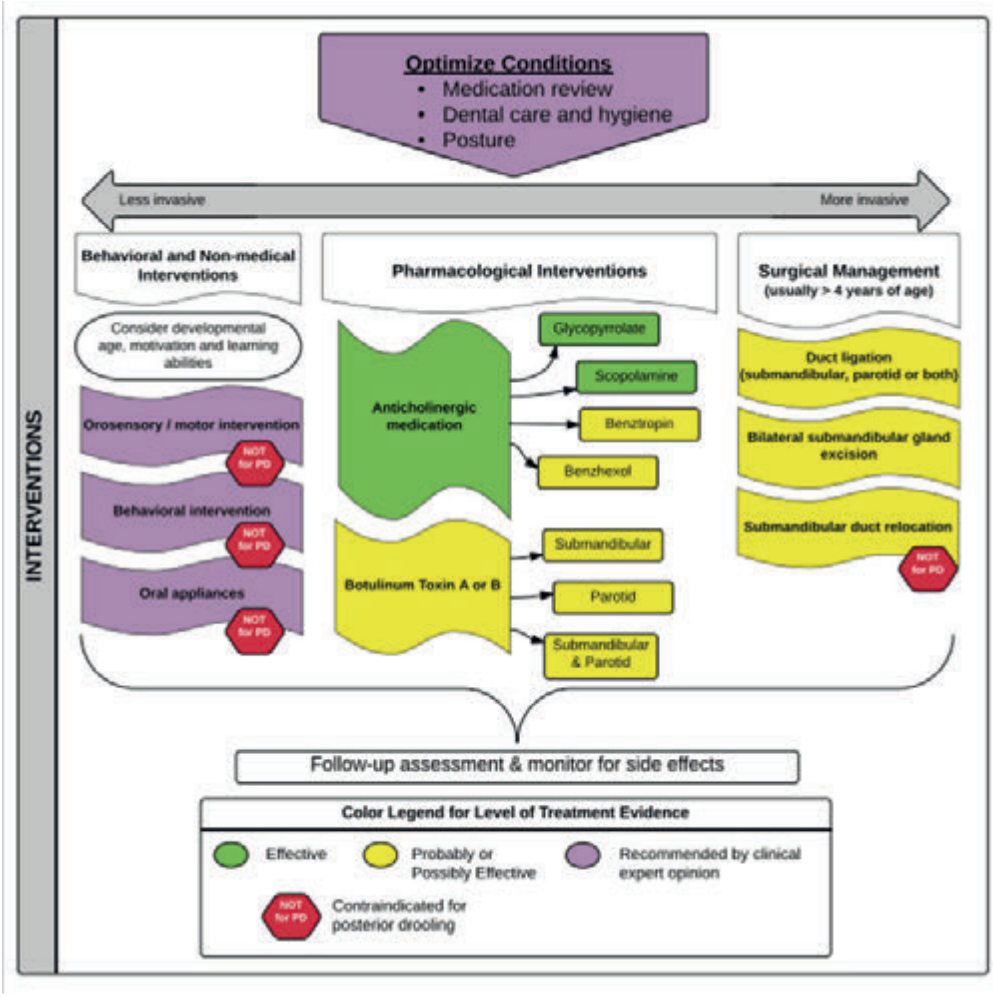
- Oromotor and orosensory strategies
  - Active and passive exercises as well as sensory applications are widely used by clinicians, although there is no agreement about the theoretical basis and effectiveness of these interventions. These approaches can be time consuming. No adverse effects are reported.
- Behavioral strategies
  - Multiple types of behavioral procedures have been shown to be effective (low level evidence). Selection and success depends on the ability of the child to comply and often requires on-going effort for maintenance of effect. No adverse effects are reported.
- Oral appliances
  - Compliance can be challenging and nose breathing must be possible for the child wearing the appliance. Children with seizure disorders may be at risk for oral injury. There is some low-level evidence that oral appliances may be effective.
- Anti-cholinergic agents which inhibit salivary secretion
  - Glycopyrrolate, scopolamine (also known as hyoscine), benzhexol and benztropin are the most commonly used agents internationally. These medications, while effective, are sometimes associated with adverse side effects such as excessive thickening of secretions, urinary retention, constipation, headache, blurred vision and behavioral disturbance.
- Intraglandular Botulinum toxin injections to the submandibular +/- parotid glands
  - Injections are often considered after inadequate response to anti-cholinergic treatment. They can be effective but need to be repeated regularly, often at 6 month intervals, and responsiveness may diminish over time. Botulinum toxin is most often injected using ultrasound guidance for assistance. Varying doses have been reported with botulinum toxin A being the most frequently used type. Side effects include irritation at the injection site, pain, hematoma, dry mouth, thickened secretions, or problems with chewing and swallowing from diffusion to the surrounding muscles thus, increasing aspiration risk.
- Surgical intervention
  - Surgery is usually reserved for patients with profuse, persistent anterior drooling, continued symptoms despite maximal conservative or pharmacological treatment, and patients with posterior drooling who have chronic aspiration and/or recurrent respiratory infections. Surgical procedures may include duct ligation or rerouting, sublingual or submandibular gland excision, and varying combinations of these procedures. Success and caregiver satisfaction are variable. Duct recanalization can occur. Side effects are usually minimal but include xerostomia and wound infection.

Longitudinal management

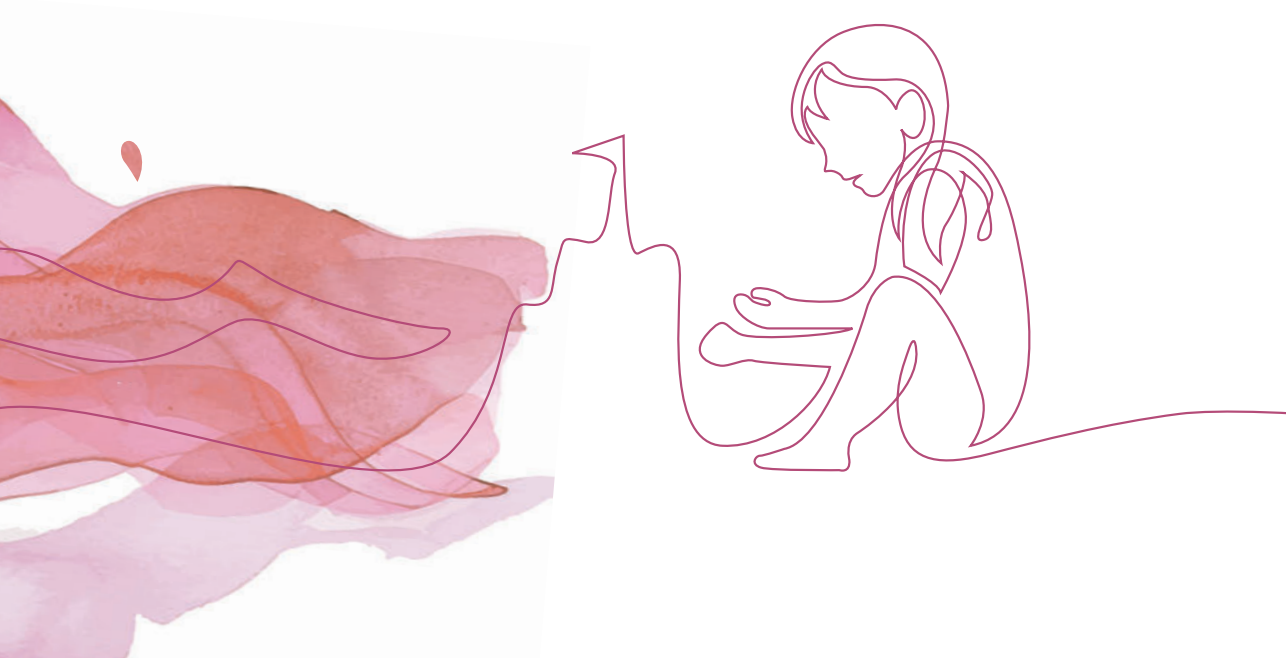
Whether or not an intervention is utilized, the psychosocial and medical effects of drooling must be monitored longitudinally. If an intervention is pursued, regular systematic monitoring of the child and caretaker for indications of efficacy and potential side effects is imperative.

Flow diagram for Evidence-Informed Clinical Practice Guideline for Sialorrhea In Children/Youth with Cerebral Palsy




INTERVENTIONS
Optimize Conditions
• Medication review
• Dental care and hygiene
• Posture
Less invasive
More invasive
Behavioral and Non-medical Interventions
Consider developmental age, motivation and learning abilities
Orosensory / motor intervention
NOT for PD
Behavioral intervention
NOT for PD
Oral appliances
NOT for PD
Pharmacological Interventions
Anticholinergic medication
Glycopyrrolate
Scopolamine
Benztropin
Benzhexol
Botulinum Toxin A or B
Submandibular
Parotid
Submandibular & Parotid
Surgical Management
(usually > 4 years of age)
Duct ligation (submandibular, parotid or both)
Bilateral submandibular gland excision
Submandibular duct relocation
NOT for PD
Follow-up assessment & monitor for side effects
Color Legend for Level of Treatment Evidence
Effective
Probably or Possibly Effective
Recommended by clinical expert opinion
NOT for PD
Contraindicated for posterior drooling

Appendices



NEDERLANDSTALIGE SAMENVATTING

Hoofdstuk 1

De glandula submandibularis is verantwoordelijk voor het grootste percentage van de speekselproductie. Het is dan ook aannemelijk dat het verwijderen van deze speekselklieren door middel van een 'bilateral submandibular gland excision' (SMGE) een positief effect heeft op kwijlen. Speeksel geproduceerd door de glandula submandibularis kan gereduceerd worden op verschillende manieren: 1) door het blokkeren van de neurologische innervatie (bijvoorbeeld met intraglandulaire botuline toxine injecties); 2) door het verleggen (submandibular duct relocation, SMDR) of onderbinden (ductus ligatie, 2-DL) van de afvoergang (ductus Whartoni) van de glandula submandibularis of 3) door het verwijderen van de glandula submandibularis in zijn totaliteit (SMGE). Het verleggen van de ductus Whartoni (SMDR), werd tot op heden veelal gezien als de eerste keuze behandeling bij ernstig zichtbaar speekselverlies (anterieur kwijlen) indien een chirurgische behandeling nodig geacht werd.

In het eerste hoofdstuk onderzochten we het objectieve en subjectieve resultaat van SMGE op anterieur kwijlen in kinderen. De mate en ernst van het kwijlen kan worden uitgedrukt in subjectieve en objectieve uitkomstmaten. Als subjectieve uitkomstmaat werd gebruik gemaakt van de Thomas-Stonell and Greenberg Classificatie, waarin onderscheid kan worden gemaakt tussen de 'Drooling Severity' en 'Drooling Frequency'. Daarnaast is er een subjectieve visuele analoge schaal (VAS, range 0-100) voor de ernst van het zichtbare kwijlen over de afgelopen twee weken, beoordeeld door ouders en verzorgers. Als objectieve uitkomstmaat hanteerden we de Drooling Quotient (DQ). Deze maat wordt geobjectiveerd door gespecialiseerde logopedisten. De DQ geeft weer welk percentage van een vastgestelde tijd er sprake is van zichtbaar speekselverlies.

Bovengenoemde uitkomstmaten werden bij elke patiënt geëvalueerd op drie tijdsmomenten: voorafgaande (baseline) aan SMGE, en zowel 8 als 32 weken na de interventie. We spreken van een 'klinisch succesvol' resultaat indien er ≥ 50% afname is van de objectieve DQ en/of een afname van 2 standaarddeviaties op de subjectieve VAS na interventie. We vonden een significante afname van zowel DQ als VAS op 8 en 32 weken. Dit resulteerden in een succespercentage van 63% na 32 weken.

Op basis hiervan concludeerden we dat het verwijderen van de glandula submandibularis een effectieve behandeling is voor kwijlen bij kinderen en adolescenten met een neurologische ontwikkelingsstoornis. SMGE kan dan ook gezien worden als een alternatieve behandeling voor anterieur speekselverlies indien een SMDR gecontra-indiceerd is.

Hoofdstuk 2

In hoofdstuk 1 zagen we dat het objectieve effect van een SMGE tot 32 weken bij het merendeel van de patiënten goed aanhield, echter we zagen ook een afname van het subjectieve effect tussen 8 en 32 weken postoperatief. Dit was de aanleiding voor een lange-termijn studie, waarin we hebben bekeken

of het subjectieve effect van SMGE over verloop van tijd aan bleef houden of verder afnam. Als primaire uitkomtmaat hanteerden we de VAS voor anterieur kwijlen en de 'Thomas-Stonell and Greenberg' classificatie.

We evalueerden het effect in een historisch cohort van 61 patiënten door middel van een vragenlijst, waarvan 35 patiënten (57%) respondeerden. De mediane follow-up duur was 313 weken (range 123-502 weken). We vonden een aanhoudend significant succes op beide subjectieve uitkomstmaten, maar we zagen ook een terugloop in het resultaat over de tijd. Zo vonden we o.a. dat 17% van de kinderen een aanvullende behandeling nodig had voor het speekselverlies op de lange termijn. Op de vraag of de ouders/verzorgers op de lange termijn een SMGE zouden aanbevelen aan lotgenoten, antwoorden echter 66% instemmend.

Op basis van deze studie konden we concluderen dat SMGE bij het merendeel van de patiënten succesvol is op de lange termijn, echter dat er een onbegrepen risico is op een hinderlijke terugloop van het effect op kwijlen en hiervoor aanvullende behandeling noodzakelijk kan zijn.

Hoofdstuk 3

Een SMGE is een extra-orale interventie en gaat dus gepaard met een zichtbaar litteken in de hals regio, net onder de kaaklijn. Dit terwijl de alternatieve chirurgische behandelingen voor kwijlen (SMDR of 2-DL) beide intra-orale behandelingen zijn, en dus geen zichtbaar litteken geven in de hals. In het derde hoofdstuk onderzochten we of het externe, zichtbare, litteken een bezwaar is voor deze behandeling in relatie tot de uitkomst van deze behandeling.

De POSAS (Patient and Observer Scar Assessment Scale) was de primaire uitkomstmaat voor deze studie. Deze gevalideerde vragenlijst werd verstuurd naar 26 ouders en verzorgers, waarvan er 25 respondeerden. De littekens werden tevens beoordeeld door een geblindeerde hoofd-hals chirurg aan de hand van foto's van de littekens gemaakt door ouders/verzorgers.

Van de ouders en/of verzorgers beoordeelden 96% de littekens als acceptabel en 19 van de 25 waren over het algeheel tevreden met de uitkomst van de behandeling. Er werd geen correlatie gevonden tussen de uitkomst van de behandeling en tevredenheid met de littekens. Succes, was zoals verwacht, gecorreleerd met een afname op de 'Thomas-Stonell and Greenberg' classificatie en met een afname van luchtweginfecties in het geval van posterieur kwijlen.

We concludeerden dat de externe littekens geen bezwaar hoeven te zijn voor deze behandeling. Dit is een belangrijke aanvulling tijdens onze informed consent procedure, wanneer er samen met ouders/verzorgers gekozen moet worden voor een extra- of intraorale chirurgische benadering.

Hoofdstuk 4

Er zijn twee chirurgische alternatieve behandelingen voor SMGE: 2-DL (two-duct ligation, ofwel het onderbinden van de ductus Whartoni) of SMDR (submandibular duct relocation, ofwel het verleggen van de ductus Whartoni). Alle behandelingen hebben hun eigen voors- en tegens. Zo heeft 2-DL een kortere operatieduur, en is na SMDR één nacht geïntubeerde opname ter observatie van de luchtweg op de Intensive Care Unit aanbevolen. Daarnaast is er een minder invasief alternatief, namelijk intra-glandulaire botuline toxine injecties. Het effect van deze injecties werkt echter uit over de tijd, en herhaaldelijke injecties onder algehele narcose zijn dan ook vaak noodzakelijk. Over het effect van botuline toxine injecties, SMDR en SMGE op anterieur kwijlen was reeds bewijsvoering in verscheidene wetenschappelijke publicaties, voor de behandeling van anterieur kwijlen door middel van 2-DL was nog weinig tot geen bewijsvoering bekend.

In dit hoofdstuk onderzochten we het effect van intra-glandulaire botuline toxine injecties in vergelijking met 2-DL voor de behandeling van anterieur kwijlen. Als primaire uitkomstmaat werd gekeken naar het behandeleffect op basis van een algemene succesdefinitie: ≥50% afname van DQ of VAS na 32 weken. We vergeleken wederom een baseline meting met het effect na 8- en 32 weken. Drieënvijftig patiënten met een gemiddelde leeftijd van 11 jaar werden geïncludeerd in de analyse. Na 8 weken zagen we een algemeen succespercentage van 88%. Na 32 weken vonden we een significant verschil tussen het behandeleffect met 2-DL en botuline toxine injecties (63% succes na 2-DL en 27% succes na botuline toxine injecties). Het behandeleffect nam dus aanzienlijk af over de tijd. Deze afname konden we niet met zekerheid verklaren. Daarnaast zagen we na 2-DL meer 'adverse events' en postoperatieve klachten in vergelijking met intra-glandulaire botuline toxine injecties.

We concludeerden in deze studie dat 2-DL een effectievere behandeling is dan botuline toxine injecties voor anterieur kwijlen, echter met een hoger risico op postoperatieve klachten en complicaties. Bovendien is er een risico op een afname van het effect tussen 8 en 32 weken na de ingreep.

Hoofdstuk 5

In eerdere hoofdstukken zagen we dat er in een aanzienlijk percentage sprake is van een afname van het behandeleffect op kwijlen, en de chirurgische behandeling daarmee niet succesvol is. Dit hoofdstuk heeft als doel het effect van revisie chirurgie te beoordelen. Er zijn verschillende theorieën waarom een chirurgische behandeling voor kwijlen niet succesvol zou kunnen zijn. Zo kan er sprake zijn van chirurgisch falen na 2-DL, doordat er alternatieve afvoergangen worden gevormd die in de mond uitkomen of kan er sprake zijn van compensatoire toename van speekselvloed door de andere speekselklieren. Daarnaast zijn er ook nog een scala aan andere patiënt gerelateerde factoren die theoretisch een belangrijke rol kunnen spelen op de ernst van het kwijlen, te denken aan o.a. houding, mondmotoriek en comorbiditeit (allergieën, gastro-oesofageale reflux etc.).

In deze studie hebben we 10 patiënten, waarbij de primaire behandeling een teleurstellend effect gaf, verder geanalyseerd. Bij alle patiënten was de primaire behandeling gericht op de ductus Whartoni, de afvoergang van de glandula submandibularis. Acht patiënten ondergingen 2-DL als primaire behandeling, 2 patiënten SMDR. We onderzochten of een herbehandeling aan de glandula submandibularis, door middel van SMGE een vermindering van het kwijlen gaf. Deze behandeling werd uitgevoerd in 7 patiënten. In de overige patiënten werd een behandeling aan de glandula parotis uitgevoerd; de afvoergang werd onderbonden. Na 32 weken bleek een herbehandeling slechts bij 3 patiënten succesvol te zijn, gedefinieerd als een vermindering van 50% op de VAS en/of DQ op 32 weken post-interventie. Er werd geen verschil gevonden tussen de techniek van herbehandeling.

Een referentie cohort werd gebruikt om te controleren voor klinische variabelen. Er waren significant meer gevallen met ernstige malocclusie (50% vs. 21%, P=0.047) en zeer ernstige spraakstoornissen (80% vs. 42%, P=0.042) in het huidige cohort.

We concluderen dat het hoge recidiefpercentage hoogst waarschijnlijk niet alleen wordt veroorzaakt door chirurgisch falen of de vorming van alternatieve afvoergangen, omdat een SMGE als revisie chirurgie niet leidde tot een behandelsucces. De klinische variabelen malocclussie en spraakstoornissen zouden de uitkomst kunnen beïnvloeden, echter is hiervoor aanvullend onderzoek noodzakelijk. Daarnaast is aanvullend onderzoek nodig om te onderzoeken of er sprake is van compensatoire hypersalivatie door o.a. de glandula parotis na submandibulaire klierchirurgie.

Hoofdstuk 6

We maken onderscheid tussen anterieur (zichtbaar) kwijlen en posterieur kwijlen. Over de behandeling van anterieur kwijlen is reeds veel onderzoek verricht. Posterieur kwijlen is daarentegen een veel minder bekend fenomeen. We spreken van posterieur kwijlen indien speeksel over de tongbasis naar de oropharynx loopt, zonder adequate slikreflex. Er is sprake van een verhoogde kans op speeksel aspiratie en daarmee gepaard gaande recidiverende luchtweginfecties en blijvende longschade.

We onderzochten in dit hoofdstuk het effect van submandibulaire klierchirurgie op posterieur kwijlen. We vergeleken drie soorten behandelingen: SMGE, 2-DL en intra-glandulaire botuline toxine injecties. We analyseerden 92 kinderen met een gemiddelde leeftijd van 9 jaar (range 1-21 jaar). De primaire uitkomstmaat was een VAS-score voor posterieur kwijlen (schaal 0-10). We vergeleken wederom baseline met 8- en 32 weken na behandeling. Als secundaire uitkomstmaat analyseerden we of er sprake was van een afname van luchtweginfecties.

Drieënzestig patiënten ondergingen botuline toxine injecties, 16 patiënten SMGE en 13 patiënten 2-DL. In de totale groep van 92 patiënten werd een significante afname op de VAS gezien. In een subanalyse zagen we het grootste en langst aanhoudende effect na behandeling door middel van SMGE, dit in vergelijking met de andere twee behandelingen.

We concludeerden dat in het geval van ernstig posterieur kwijlen SMGE de aanbevolen behandeling van eerste keuze is, maar dat er nog veel onderzoek nodig is op het gebied van posterieur kwijlen.

Hoofdstuk 7

Kwijlen bij kinderen verdient een multidisciplinaire aanpak. In onze kliniek is het multidisciplinaire 'Saliva Control Team' al meer dan 20 jaar actief in de behandeling van deze groep kinderen. Gedurende de jaren is er dan ook veel ervaring op gedaan en zijn er vele wetenschappelijke studies gepubliceerd. Deze ervaring en kennis heeft gezorgd voor een persoonsgerichte, geïndividualiseerde benadering van elke patiënt. In dit hoofdstuk presenteerde we onze ervaring over de afgelopen jaren, waarin we in 20 jaar tijd 1643 consulten hebben verricht en 816 patiënten behandelden.

We begonnen in 2000 met de behandeling van kwijlen door middel van intraglandulaire botuline toxine injecties en hebben ons palet aan behandelingen gedurende de jaren langzaam verder uitgebreid. We leerden onder andere dat een chirurgische behandeling voor anterieur kwijlen op zijn plaats is vanaf de leeftijd van 10-12 jaar. We zagen ook dat SMGE over de jaren toenemend populair werd, enerzijds doordat we er meer ervaring mee opdeden, maar bovenal omdat het nagenoeg even effectief bleek te zijn als SMDR. Daarnaast nam de populariteit van deze ingreep toe door zijn relatieve simpliciteit, korte opname duur en de toenemende bekendheid als eerste keuze behandeling voor posterieur kwijlen. De minder invasieve ductus ligaties toonden tevens een stijgende lijn; echter ten gevolge van een onbegrepen hoog recidief percentage is de positie van deze behandeling nog niet geheel duidelijk.

Concluderend, presenteerden we in dit hoofdstuk onze ervaringen door de jaren heen. We zagen o.a. dat: 1) er over de jaren meerdere chirurgische behandelingen zijn ontwikkeld voor kwijlen, ieder met zijn eigen indicaties, 2) ons team steeds bewuster en beter is in persoonsgerichte zorg en 3) het multidisciplinaire karakter van ons team essentieel is voor een goede behandelkeuze en evaluatie hiervan.

Discussie en conclusie

In dit proefschrift onderzochten we het effect van SMGE op anterieur en posterieur kwijlen in kinderen met een neurologische ontwikkelingsstoornis.

We kunnen concluderen dat een bilaterale glandula submandibularis extirpatie de primaire behandeling is indien er sprake is van 1) ernstig zichtbaar kwijlen met een progressieve faryngeale slikstoornis, voorbij de leeftijd van 10-12 jaar; 2) indien een rerouting van de ductus Whartoni om welke reden dan ook gecontra-indiceerd of niet gewenst; 3) in het geval er sprake is van posterieur kwijlen.

Tijdens het schrijven van dit proefschrift zagen we ook enkele hiaten, welke aandacht behoeven in toekomstig wetenschappelijk onderzoek. Zo beschreven we het onderbelichte probleem van posterieur kwijlen, een aandoening welke kan leiden tot blijvende longschade én waar nog altijd veel kinderen met een cerebrale parese aan komen te overlijden. Vroegtijdige herkenning en behandeling is dan ook

essentieel. Herkenning van posterieur kwijlen is echter zeer uitdagend voor zowel ouders/verzorgers als professionals, aangezien symptomen niet altijd even evident zijn en aanvullende diagnostiek moeilijk uitvoerbaar is. Het is dan ook van hoge prioriteit dat er de komende jaren onderzoek gedaan wordt naar deze aandoening en de effecten van verschillende behandelingen, o.a. op de langere termijn.

Ten tweede is het nog altijd niet duidelijk waarom er sprake is van een groot recidief percentage van kwijlen na primaire behandeling, zoals meerdere malen naar voren komt in dit proefschrift. In ons behandelteam proberen we te werken naar het kunnen voorspellen van succes per individu, dan wel falen van een behandeling. Er zijn verschillende theorieën waarom het elimineren van submandibulair speeksel door het verwijderen van deze klieren onvoldoende helpt, echter bewijsvoering ontbreekt. Het ontwikkelen van een behandelprotocol voor 'non-responders' door toekomstig onderzoek is dan ook zeer gewenst, en sluit aan op onze persoonsgerichte benadering.

Dit proefschrift is slechts een puzzelstukje in de ontwikkeling van een gepersonaliseerde benadering voor de behandeling van kwijlen. We hebben laten zien dat een glandula submandibularis extirpatie een belangrijke behandeling is voor zowel anterieur als posterieur kwijlen. Er zijn echter nog vele vragen welke een antwoord behoeven, met name op het gebied van posterieur kwijlen.


A

DATA MANAGEMENT FORM

General information about the data collection

This research project involves human subject data. Oral or written informed consent for collecting such data was obtained from the participants and/or from their parents (or legal representatives) for those younger than 18 years old. All studies were performed in accordance with the principles of the Declaration of Helsinki. The medical and ethical review board Committee on Research Involving Human Subjects Region Arnhem Nijmegen, Nijmegen, the Netherlands has given approval to conduct these studies.

FAIR principles

Findable

Data were initially collected and stored in a secure "drooling" database (named DROOLING_ TBL_2007. MDB), which now serves as a back-up. Access to this database is protected by the department of Rehabilitation of the Radboud university medical center. Documentation (i.e., read me file) to describe the datasets is provided on the department server. All necessary anonymized data for each study is converted for subsequent analysis in SPSS.

Accessible

Only members of the research group have access to the database. Paper records are stored in the department's archive. The data is not available in a public repository yet. However, all data will be available on request by contacting the corresponding author or the staff secretary of the department of Rehabilitation of the Radboud university medical center (secretariaatstaf.reval@radboudumc.nl).

Interpretable

Documentation has been added to the datasets to make them interpretable. The documentation contains links to publications, references to the location of the datasets, and a description of the datasets. The data are stored in SPSS format. No existing data standards have been used such as vocabularies, ontology's or thesauri.

Reusable

The data will be stored for at least 10 years and can therefore also be reused in this time period. There is no embargo on the accessibility of the data.

DANKWOORD

Dit is het laatste, en wellicht wel het meest belangrijke hoofdstuk van dit proefschrift. Na vele jaren gaat er een kaft om het werk en sluit ik dit hoofdstuk in mijn carrière. Ik kijk terug op een zeer leerzame periode, met vallen en opstaan. Ik ben dankbaar wat dit proefschrift mij heeft gebracht, zowel professioneel, maar nog meer als mens.

Dit proefschrift is tot stand gekomen dankzij hulp, inzet, samenwerking en engelengeduld van vele personen. Iedereen die een bijdrage heeft geleverd wil ik hiervoor dan ook bedanken. Een aantal personen in het bijzonder.

Geachte Dr. F.J.A. van den Hoogen, beste Frank, altijd heb je vertrouwen gehouden in het succesvol afronden van dit proefschrift. Dit eeuwige vertrouwen, geduld en meebewegen met de fases van mijn carrière en persoonlijke leven, hebben geleid tot dit succes. Je bent de motivator die ik nodig had. Naast promotor was je ook mijn opleider. De vele gesprekken over wetenschappelijk onderzoek, opleiding en carrière coaching zijn goud waard. Je weet de juiste snaar te raken en hebt altijd aandacht gehad voor mij als persoon. Ik ben je heel erg dankbaar en kijk er naar uit mijn carrière als collega's voort te mogen zetten in het Radboudumc.

Geachte Dr. C.E. Erasmus, beste Corrie. De eerste jaren van mijn wetenschappelijke carrière brachten we veel tijd samen door op de drooling poli. Je holistische kijk op de patiënt viel meteen op, en is bewonderingswaardig. Dank voor je tomeloze inzet, je altijd snelle reacties op vele mailtjes, en voor je geduld in het begeleiden van dit proefschrift.

Karen van Hulst, jij zorgde de eerste jaren van mijn onderzoek voor een warm nest. Ik bracht uren door in je werkkamer, om alle data uit de dossiers te verzamelen, en jij werkte rustig om mij heen. Je bent een positief mens, het glas is altijd halfvol, en dat vind ik fantastisch. Je bescheidenheid siert je, want jij hebt veel fundamenteel en belangrijk onderzoek verzet voor ons team. Daarnaast ben je (samen met een gepassioneerd team logopedisten) de uitvoerende kracht achter vele metingen die de basis zijn voor al het wetenschappelijk onderzoek in dit proefschrift. Jouw constructieve, opbouwende feedback en ervaring als epidemioloog zijn heel belangrijk geweest voor het tot stand brengen van vele artikelen. Ik ben heel erg dankbaar en vereerd dat we dit hoofdstuk nu samen mogen sluiten.

Beste Speeksel Controle Team Nijmegen, Drooling Team. Het is bijzonder hoe een multidisciplinair team al zolang consistent is en vol passie samenwerkt om deze niche van zorg te verbeteren. Ik denk dat er weinig teams zijn zoals deze. Dank voor jullie inzet en geduld. Beste Saskia en Stijn. Allen werkten we aan dezelfde trial, en allen ronden we een mooie promotie af op dit onderwerp. Bedankt voor de fijne samenwerking.

Ouders, zorgverleners en kinderen die we hebben behandeld over de afgelopen jaren. Dank voor jullie participatie en vertrouwen in onze visie. Zonder jullie was dit proefschrift niet tot stand kunnen komen.

Vele master studenten, o.a. Eva, Carleen, Tieneke en Mirthe. Jullie hebben een mooie bijdrage geleverd aan de artikelen in dit proefschrift, en ik heb van jullie mogen leren over de kunst van superviseren en loslaten. Dank hiervoor.

Graag wil ik de leden van de beoordelingscommissie hartelijk bedanken voor het beoordelen van het proefschrift.

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Beste otologen, ik kijk er naar uit om mijn ambities samen met jullie te ontplooien. Samen verzetten we het harde werk en ondersteunen we elkaar waar nodig. Ik kijk er naar uit om samen de weg naar innovatie te gaan bewandelen. Het is elke dag een feest om te mogen werken in dit team vol inspirerende mensen.

Team schedelbasis, in het bijzonder Dirk en Thijs. Sinds kort mag ik veel van jullie leren en werken we samen aan de beste zorg. Ik ben trots onderdeel te zijn van jullie team, wat verzetten jullie samen veel werk. Ik kijk er naar uit mijn niche te vinden binnen de schedelbasischirurgie en de komende jaren van jullie te kunnen leren.

Beste collega's in het MUMC+, jullie gaven mij de kans mijn eerste stappen te zetten als academisch KNO-arts. Het was van korte duur, maar ik kijk terug op een hele leerzame, warme tijd. Dank hiervoor.

Alle (oud) arts-assistenten KNO, dankjewel voor de gezellige uren in de assistentenkamer, weekenden samen en steun gedurende mijn opleiding. Wat was het een bijzondere tijd.

De vakgroep KNO van het VieCuri MC en het Jeroen Bosch Ziekenhuis in het bijzonder wil ik bedanken voor jullie steun en vertrouwen in mijn opleiding tot KNO-arts, en ook als jonge klare. Ik heb veel van jullie mogen leren.

Lieve Karen, onze vriendschap gaat heel ver terug. We hebben elkaar in alle keuzes door de jaren heen gevolgd, soms raakten we elkaar even kwijt, maar altijd kwam dat weer goed. De basis van onze

vriendschap is sterk. Onze levens kennen veel gelijkenissen, en dat zorgt voor hele fijne gesprekken. Ik hoop dat we nog vele mooie mijlpalen in ons leven samen mogen vieren. Dank voor de heerlijke momenten van ontspanning, vele kopjes koffie en wijntjes, fantastische feestjes, en dat jij nu als paranimf aan mijn zijde wil staan. Dat onze vriendschap voor eeuwig mag duren.

Lieve Ellen, Steffie, Lianne, Danella en José. Of eigenlijk, lieve Els, Stuf, Lies, Nel en Joets. Wat hebben we mooie momenten met elkaar beleeft. Jullie hebben mijn middelbareschooltijd en studententijd tot een succes gemaakt. We delen dezelfde humor, en natuurlijk onze Limburgse roots. Het is altijd een feest om weer in Venlo te zijn, al zijn die momenten door de afgelopen jaren veel te schaars. Toch waren jullie er altijd voor mij, en weet ik dat ik bij jullie terecht kan. Jullie brengen mij terug naar de meest memorabele avonden, die een lach op mijn gezicht toveren. Als we elkaar zien en spreken is het altijd meteen goed, tekenend voor onze vriendschap en het respect voor elkaar. Ik kijk er naar uit om na het afronden van dit proefschrift meer tijd met jullie door te brengen en weer nieuwe herinneringen te maken voor de rest van ons leven.

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Lieve familie Habraken, wat heb ik een geluk met zo'n fijne schoonfamilie. Hoe vaak stelden jullie wel niet de vraag: "Hoe is het eigenlijk met je promotie?". Daar komt nu een einde aan. We beleven mooie momenten met elkaar, gaan weekenden samen weg en genieten van al het kleine kroost. In het bijzonder wil ik Guus en Liesbeth bedanken voor jullie steun voor mij, maar nog veel meer als fantastische opa en oma voor Sara en Doortje.

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ABOUT THE AUTHOR

Corinne Petronella Antoinette Delsing was born on the 2nd of January 1987 in Venlo, the Netherlands. In 2005 she graduated from secondary school at the Valuascollege Venlo. In 2006 she finished a bachelor's degree in nursing, after which she started medical school at the Radboud University in Nijmegen. Following her undergraduate studies, she moved to Australia for a research internship in the field of gynecology. Her fourth-year medical internship inspired her to pursue a career in the field of Ear, Nose and Throat surgery (ENT). She graduated from medical school in 2012 and started working as a resident at the department of Intensive Care Medicine (ICU). During her work in the ICU department, she was also engaged in several research projects within the department of ENT, under the supervision of Dr. F.J.A. van den Hoogen. After a year in the ICU department, she started working as a PhD candidate. During the first year she received a grant for research in the field of submandibular gland surgery for drooling. In 2015, Corinne started her residency at the Department of Otorhinolaryngology and Head and Neck Surgery of the Radboudumc, with a special interest in otology and skull base surgery. In 2022 Corinne finished her training and started working as an ENT specialist at the MUMC+ in Maastricht. After this first experience as a junior consultant, she moved to Australia with her husband and two daughters to continue her surgical training with an otology fellowship, with a focus on endoscopic ear surgery and cochlear implantation.

From August 2023 Corinne is working as an otologist at the Radboudumc. She has a special interest in teaching and recently joined the Academic Alliance Skull Base Pathology Radboudumc – MUMC+. Corinne lives in Nijmegen with her husband Mathieu and two daughters, Sara and Doortje.

PHD PORTFOLIO

PhD portfolio of C.P.A. Delsing

Department: **Otorhinolaryngology**

PhD period: **01/12/2013 – 22/11/2024**

PhD Supervisor(s): **Dr. F.J.A. van den Hoogen**

PhD Co-supervisor(s): **Dr. C.E. Erasmus, Dr. C.C.M. van Hulst**

Training activities	Hours
Courses	
- RU - Statistics for PhD's by using SPSS (2012)	60.00
- RIHS - Introduction course for PhD candidates (2014)	15.00
- RU - Digital Tools (2014)	4.00
- Radboudumc - Scientific integrity (2015)	20.00
- RU - Education in a Nutshell (2015)	28.00
- Radboudumc - eBROK course (2015)	42.00
- RU - Scientific Writing for PhD candidates (2015)	84.00
- Radboudumc - Scientific integrity (2016)	20.00
- RU - Mindfulness Based Stress Reduction (2017)	45.00
- Radboudumc - Introduction day (2024)	6.00
- RU - Statistiek voor promovendi met SPSS (2024)	60.00
Seminars	
- Grand Rounds and research rounds Radboudumc (2024)	14.00
Conferences	
- Oral Presentation Dutch Conference ENT (2017)	14.00
- Oral Presentation Dutch Conference ENT (2022)	12.00
- Meeting of Dutch ENT society (2013-2024)	112.00
Other	
- None	
Teaching activities	
Lecturing	
- None	
Supervision of internships / other	
- Training HAN Scrub Nurses (2021)	56.00
- Training of registrars (2016-2022)	84.00
- Supervision of internships Master Students (2022)	140.00
Total	**816.00**

LIST OF PUBLICATIONS

Delsing CP, Verbist BM, van den Hoogen FJ. Hersenzenuwuitval door hoofd-halstumoren [Cranial nerve palsy caused by tumours of the head and neck]. Ned Tijdschr Geneeskd. 2013;157(22):A6094. Dutch. PMID: 23714295.

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Delsing CP, van Duijnhoven M, Arnoldussen C, le Noble J. Diagnostic dilemmas in a patient with multivascular embolic stroke. Neth Heart J. 2015 Jul;23(7-8):363-5. doi: 10.1007/s12471-015-0720-7. PMID: 26031637; PMCID: PMC4497986.

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Delsing CP, Bekkers S, Erasmus CE, van Hulst K, van den Hoogen FJ. Posterior drooling in children with cerebral palsy and other neurodevelopmental disorders. Dev Med Child Neurol. 2021 Sep;63(9):1093-1098. doi: 10.1111/dmcn.14888. Epub 2021 Apr 12. PMID: 33844298.

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