Botulinum toxin and surgery for drooling:

a study in children with cerebral palsy

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Ter nagedachtenis aan mijn vader
Voor mijn moeder

A prince who will not undergo the difficulty of understanding
must undergo the danger of trusting

George Savile, 1st Marquess of Halifax

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Chapter 1

Introduction

Drooling (sialorrhea) is physiological in children up to approximately 18 months of age. If it persists beyond the age of four years, it is commonly considered pathological and is usually a symptom of underlying neurological conditions such as cerebral palsy (a heterogeneous group of non-progressive motor disorders caused by chronic brain injuries that originate in the prenatal period, perinatal period, or first few years of life) or infantile encephalopathy.

As a symptom, it is frequently under-estimated. To the uninitiated, the mere loss of saliva might be considered a minor hindrance when compared to the other disabilities these children must cope with, which includes severe motor disorders and –often- cognitive impairment. Clinical practice has shown this is not the case, however. According to one author, "the distress and social stigma of continuous drooling is so disturbing even to the moderately retarded child that many consider it their worst affliction".[1]

It is also among the most common dysfunctions in children with cerebral palsy. Earlier estimates suggest between 10-37% of all children with cerebral palsy suffer from unwanted saliva loss.[2] A more recent, systematic study of children attending special schools found a prevalence of 58%, with 33% suffering from severe drooling (characterized by the dripping of saliva onto clothing).[3] This study also found that the degree of drooling fell as a child's dental age progressed, with 75% of children with primary dentition drooling, compared to 43% of children with permanent dentition.

As a result, there has been increasing scientific and clinical attention for the management of this problem. As this thesis covers certain aspects of the invasive management of drooling, the following paragraphs will cover the etiology and morbidity of drooling, as well as current treatment strategies.

SALIVA PRODUCTION, SWALLOWING AND DROOLING

Humans produce approximately 1-1.5 liters of saliva each day, with a significant day-to-day variation, as well as a circadian (24-hour) and circannual (yearly) rhythm. Saliva production is low while asleep, and peaks during stimulation (eg. meals). Circadian flow variations affect not only the amount but also the constitution of saliva.[4] Overall salivary flow is highest in winter and lowest in summer.

Whole saliva is composed of a variety of electrolytes, as well as immunoglobulins, proteins, enzymes, mucins, and nitrogenous products (eg. urea and ammonia).

Saliva has 5 major functions that serve to maintain homeostasis in the oral cavity: (1) lubrication and protection, (2) buffering and clearance of ingested chemicals, (3) maintenance of tooth integrity, (4) antibacterial activity, and (5) taste and digestion.[4]

The vast majority of saliva in humans is produced in the acinar cells of the paired parotid, submandibular and sublingual glands (figure 1). Additionally, hundreds of accessory salivary glands line the oral mucosa and add another 5% to the total daily salivary production. All salivary glands produce serous, mucous or mixed (sero-mucous) secretions, in varying proportions depending on gland anatomy and stimulation.

The submandibular (or: submaxillary) gland is the second largest salivary gland. At rest, it produces the vast majority of overall saliva (approximately 65-70%).[5] It comprises both serous and mucous cells, with the latter generally the most active. The gland lies in the submandibular triangle, formed by the anterior and posterior bellies of the digastric muscle and the inferior margin of the mandibula. It wraps around the mylohyoid muscle to be divided into a smaller superficial lobe and larger deep lobe (figure 1). Submandibular saliva is delivered via the submandibular duct (or: Wharton's duct), which is approximately 5cm long. The duct exits from the medial surface of the gland and travels between the mylohyoid and hyoglossus muscles onto the genioglossus muscle. It opens into the floor of the mouth laterally to the lingual frenulum, forming the sublingual caruncle.

Like other salivary glands, the submandibular gland receives both sympathetic and parasympathetic innervation. Parasympathetic innervation is through the chorda tympani (a branch of the facial nerve), which anastomoses and runs with the lingual nerve until the submandibular ganglion. Sympathetic nerve fibers to the submandibular gland originate in the superior cervical ganglion and travel with the lingual artery to the gland. Although saliva from the submandibular gland is usually relatively mucous in nature, varying the balance between parasympathetic and sympathetic activity can alter the consistency of saliva produced. Parasympathetic stimulation produces a serous (watery), enzyme rich secretion. Sympathetic stimulation lowers the gland's blood supply, thus reducing the potential for water collection and resulting in the production of a more mucous, glycoprotein rich secretion.

The sublingual glands are closely associated with the submandibular glands, as they share part of their innervation and drainage. Producing approximately 7-8% of resting saliva, they are the smallest of the major salivary glands, and mostly comprise mucous acinar cells. The sublingual glands lie just below the mucosa of

the floor of the mouth, anteriorly to the submandibular gland. They are bordered by the mandibula and genioglossus muscles laterally, and the mylohyoid muscle inferiorly. Unlike the other major salivary glands, the sublingual glands lack a true fascial capsule. Saliva from the gland is delivered via approximately 10 small ducts of Rivinus, which exit the gland superiorly and open intraorally along the plica fimbriata, laterally to the lingual frenulum. A larger duct (of Bartholin) may join the nearby submandibular duct to the drain through the sublingual caruncle.

The parotid gland is the largest salivary gland, and is mainly active following tactile or gustatory stimulation. At rest, it is responsible for approximately 20% of total saliva; when stimulated, this rises to over 50%. As its acinary cells are mainly of the serous secreting type, it produces a watery secretion that facilitates mastication and swallowing and begins the digestion of starches. The glands are positioned in the pre-auricular region, extending from the zygomatic arch to the angle of the mandible. The facial nerve passes through the gland and divides it into a superficial and deep portion. Secretions from the parotid gland are delivered via the parotid duct (or: Stenson duct), which arises from the anterior portion of the gland. The duct is 4-6cm long and runs anterior to the masseter muscle, turns medially to pierce the buccinator muscle, and ultimately has its papilla just opposite the second upper molar in the posterior portion of the oral cavity (figure 1).

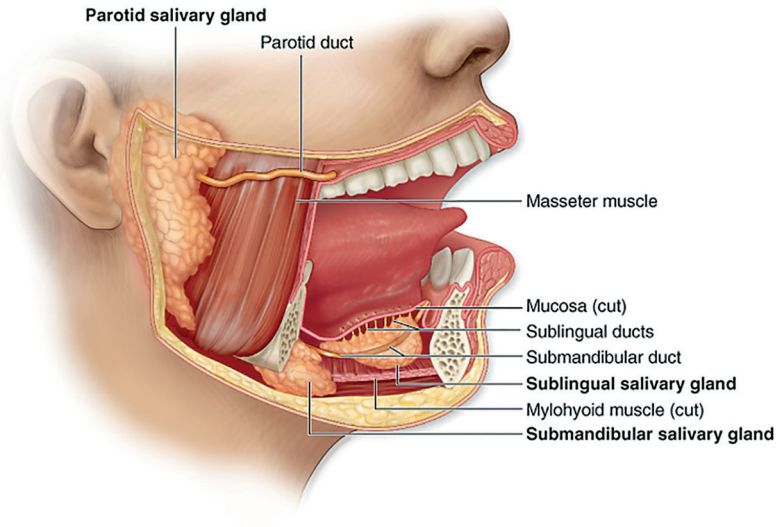


Figure 1 In descending order of size, the main salivary glands are the parotid glands, submandibular (or: submaxillary) glands and sublingual glands.

As with the submandibular gland, secretion of saliva is controlled by both parasympathetic and sympathetic nerves. The balance between these two determines both the amount and the consistency of produced saliva, with parasympathetic stimulation leading to large amounts of serous secretion. Parasympathetic innervation runs via the auriculotemporal nerve (a branch of the trigeminal nerve), whereas sympathetic innervation originates in the superior cervical ganglion and travels from the external carotid nerve plexus along with the external carotid arterial branches.

As saliva is produced throughout the day, the vast majority has to be swallowed. The normal passage of saliva from the mouth to the oesophagus is dependent upon cognitive awareness of social norms, intact oral sensitivity, and a well-developed coordination of oro-facial, palato-lingual, and head- and neck musculature. Problems with one or more of these systems will impair the swallowing of saliva, and cause the loss of saliva from the mouth (anterior drooling). Posterior drooling refers to the pooling of saliva in the hypopharynx, where it should normally cause a swallow reflex. In the absence of such a reflex or an adequate pharyngeal phase of swallowing, saliva may spill into the trachea (aspiration). Posterior drooling frequently presents with congested breathing, a loud rattle in the throat, and recurrent aspiration pneumonias.

In cerebral palsy, there is usually impairment of motor function and loss of functional skills caused by abnormalities in the pyramidal and extra-pyramidal tracts, resulting in an upper motor neuron syndrome. A typical clinical presentation will include impaired motor skills, combined with a variety of other problems such as mental retardation, epilepsy, and visual and auditory disorders. The normal but complex mechanism to handle saliva, outlined above, is therefore frequently impaired:

- Cognitive impairment may result in the unawareness of children that drooling is socially unacceptable.
- Decreased intra-oral sensitivity means children are unaware of loss of saliva, or lack a stimulus to swallow.[6]
- Malcoordination of muscles in the oral stage of swallowing, coupled with a lower frequency of spontaneous swallowing, leads to inadequate swallowing, excessive pooling of saliva in the anterior portion of the mouth with resultant loss of saliva.[7]
- Incomplete mouth and lip closure, as well as proclination of the upper teeth as a result of constant tongue thrusting, and poor posture or deformity of the spine and trunk facilitate the anterior leakage of saliva from the mouth.[8,9]
- Stasis of saliva sublingually and in the buccal pools can leak to the posterior side of the tongue and into the hypopharynx.

It is important to note that salivary flow rate usually does not differ between children with cerebral palsy who drool and healthy individuals. Drooling is thus primarily caused by inadequate swallowing, rather than hypersalivation.[10]

CONSEQUENCES OF DROOLING

Drooling can have serious, widely varying consequences for a person's well-being. Children with severe anterior drooling often suffer from a chronically irritated, macerated skin over the chin and peri-oral region. In cool weather, the dampness from saliva is chilling. The constant presence of saliva can impair articulation and impair communication. In rare cases there may be chronic loss of fluid and nutrients as a result of continuous drooling.[11]

Perhaps even more detrimental to the quality of life, however, are the social consequences of drooling. The unpleasant sight and odor can result in alienation from other members of society, and it has been reported that children receive fewer tokens of physical affection, even from their parents.[12] Children can be excluded from certain activities, such as cooking, drawing, of playing board games, and the stigma associated with drooling means that children are frequently underestimated with regards to their mental abilities. For caretakers, constant saliva loss can mean multiple daily bib or clothing changes, significantly increasing the burden of daily care. Damage to clothes, toys, books, and furniture has been described. In the modern age, communication aids, mobile phones, computer and audio equipment tend to be damaged as a result of exposure to copious amounts of saliva.[13]

Posterior drooling can have serious consequences to general health. Chronic aspiration may lead to recurrent pneumonias, which can be life-threatening. In severe cases, children may require multiple intensive care admissions per year.[14]

TREATMENT OF DROOLING IN CEREBRAL PALSY

Many treatment options have been attempted for drooling over the years, including correction of situational factors and posture, speech therapy, biofeedback therapy, pharmacotherapeutics, radiotherapy and a number of surgical methods. The merits of each have been subjected to debate; the wide range of techniques proposed and the poor comparability of various studies have made it difficult to establish

which approaches deserve preference over others.[15] True consensus over a universal treatment strategy has never materialized, although it appears widely agreed that children should be evaluated by a multidisciplinary team to determine the best approach in a specific case.

William Crysdale, an otolaryngologist at the Hospital for Sick Children in Ontario, Canada, was one of the first to describe such a team, which consisted of a surgeon, speech language therapist, physical therapist and dentist.[16] This approach has been copied elsewhere, although the exact formation the team has varied. For instance, the Nijmegen Drooling Consortium does not feature a dentist and physical therapist, but has a specialist in rehabilitation medicine, a behavioural specialist, and pediatric neurologist in addition to a surgeon and two speech language therapists. A multidisciplinary setup allows for a thorough evaluation of a child's condition and problems from varying perspectives, and also facilitates the development of new treatment strategies and scientific research.

Another major advantage of systematic multidisciplinary evaluation is that it allows for optimal assessment of a patient's drooling problems both before and after treatment. This deserves specific attention, as the quantification of the extent of drooling has proved difficult. A wide variety of systems have been used, from scintigraphy methods to assess the absolute amount of secreted saliva, to recordings of drooled saliva over a specific amount of time, questionnaires evaluating the impact on daily life, and simple outcome scales to determine if a patient's condition was 'better' or 'worse' following intervention.

We feel a combination of a number of these parameters are required to get an adequate overall impression of the extent of the problem, and the Nijmegen team therefore employs a number of tools to evaluate patients (table 1). Aside from standardized neurological and speech-language intake tools, structured assessments are taken to attempt to quantify the extent of drooling. The drooling quotient (DQ), a direct-observational semi-quantitative method, provides a relatively quick overall impression of the amount of drooling. During a ten-minute sessions, the absence or presence of new saliva on the lips or chin is recorded every fifteen seconds, for a total of forty observations. The measurement is repeated after approximately one hour, and the mean of the two observations is then used to calculate the DQ, expressed as the percentage of time a child drools.

To compensate for the strong diurnal variation in drooling, parents or caretakers are also asked about the subjective frequency and severity of drooling on a standardized rating scale (table 1), and are asked to fill in a four-page questionnaire which includes

Table 1 Standardized investigations in the Nijmegen Drooling Consortium

Assessment	Purpose	Performed By	Properties	Clinical utility
Speech pathologist examination	Examination of positioning, oral functions, speech and swallowing	Speech pathologist	–	Expert opinion to support decision making on treatment/ intervention
Neurological Evaluation	Standardized examination of neurological defect and prognosis	Pediatric Neurologist	Structured, standardized inventory, not validated	Establish baseline neurological condition and prognosis
Drooling Quotient	Quantitative scores of drooling	Speech pathologist	Validated instrument to express the severity of drooling	Score on a numerical scale
Drooling Severity and Frequency Scale	Outcome on an ordinal scale	Nurse (practitioner)/ speech pathologist	Structured inventory, not validated, easy to use in clinical practice	Score which is indicative of the severity and frequency of drooling
Salivary flow	Measure saliva secretion in ml/min or g/min	Speech pathologist	Variable outcome with intra-and inter-individual variation, but reliable for research purposes with larger numbers of patients	Research purposes
Quality of Life Questionnaire and VAS-scores	Measure subjective severity of problem and influence on daily activities	Parents	Structured inventory, validated, easy to use in clinical practice	Subjective impact of problems on daily life and care

a VAS reflecting the severity of drooling during the past two weeks, as well as a number of other questions about a child's general well being.

The combined data from each of the specialists following patient evaluation ultimately leads to a treatment recommendation for an individual child. It appears generally agreed that non-invasive strategies such as behavioural therapy or speech therapy should be attempted before more invasive treatments are considered. These include intraglandular injection of botulinum toxin, and various surgical procedures.

ANTICHOLINERGIC THERAPY AND BOTULINUM TOXIN

Although the salivary glands have no inhibitory innervation, all salivary glands strongly respond to parasympathetic and sympathetic innervation. Sympathetic innervation mainly regulates the composition of saliva, whereas parasympathetic stimulation increases the secreted volume.

As parasympathetic activity is mediated by acetylcholine and corresponding receptors at the neuro-glandular junction, anticholinergic agents that inhibit this effect are an obvious method to reduce salivary flow.

Initially, systemic anticholinergics such as scopolamine, glycopyrrolate and benztropine were used and reported successful in approximately 50% of patients.[17] Although reportedly effective in reducing salivary flow and drooling, their use was associated with notable anticholinergic side effects such as restlessness, irritability or sedation, gastrointestinal problems and temporary visual impairment.

The re-introduction of botulinum toxin (in 1977) appeared to offer a solution to the problem of systemic availability of anticholinergics. A potent anticholinergic, botulinum toxin is produced by the anaerobic bacteria Clostridium botulinum and is highly toxic.[18] To date, seven subtypes have been described, which mostly differ in antigenic properties (table 2).

Although systemic availability of botulinum toxin causes widespread paralysis known as botulism, localized injection causes a highly localized denervation of the target organ. Several clinical applications have been developed for botulinum toxin, both cosmetic (denervation of facial muscles reduces wrinkles) and functional (hyperhidrosis). Type-A neurotoxin is used most frequently by far.

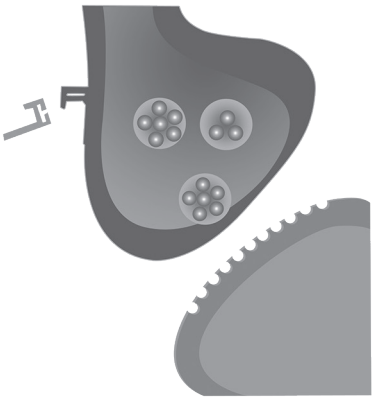
Table 2 Botulinum Toxin Types, Target Sites, Discoverers, and Year Discovered

Type	Target	Discoverer	Year
A	SNAP-25	Landman	1904
B	VAMP	Ermengem	1897
C	Syntaxin	Bengston & Seldon	1922
D	VAMP	Robinson	1929
E	SNAP-25	Gunnison	1936
F	VAMP	Moller & Scheibel	1960
G	VAMP	Gimenez & Ciccarelli	1970

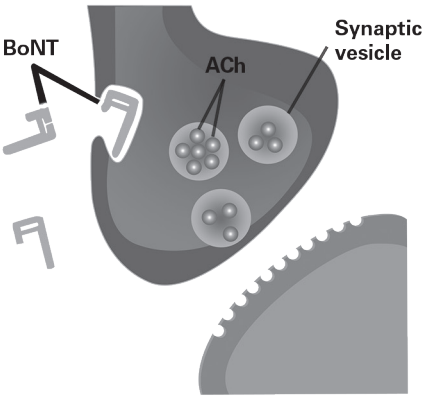
Type-A toxin, when injected into a target organ, irreversibly couples to the plasma membrane of cholinergic terminal nerve endings (figure 2a). The toxin is then internalized in a vesicle via endocytosis (figure 2b), after which translocation occurs and the toxin is released into the cytosol (figure 2c). Once there, type-A toxin cleaves the SNAP-25 enzyme (synaptosomal-associated protein with a molecular weight of 25 kDa).[19] This cytoplasmic protein is located at the cell membrane of the terminal nerve ending, and is required for the release of acetylcholine. Consequently, cleaving SNAP-25 prevents the release of acetylcholine and results in functional denervation of the target organ. Restoration of function and reinnervation are realized by axonal sprouting (figure 2d).

Following the increasing usage of botulinum toxin for conditions such as hyperhidrosis, various specialists suggested its use for saliva control issues.20-22 The first case reports followed shortly after the turn of the millennium.23,24 A number of subsequent controlled and uncontrolled trials demonstrated it reduced salivary flow by approximately 40%, and led to a clinically relevant reduction in drooling in approximately 50% of patients.[25-29]

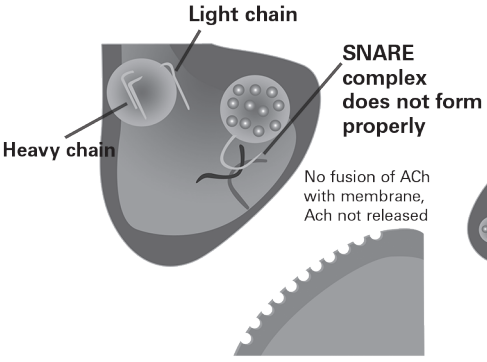
In children, botulinum toxin is usually administered under general anesthesia, using ultrasound guidance to identify the salivary glands. Although some authors have chosen to inject both the submandibular and parotid glands, the largest studies have limited injection to the submandibular glands, a decision based on the premise that these are responsible for the majority of resting saliva. Additionally, limiting injection to the submandibular glands means that the parotids continue to function normally to facilitate mastication and digestion. In most papers, botulinum toxin appears to show a maximum effect after 2-8 weeks, and lasts for approximately six months.



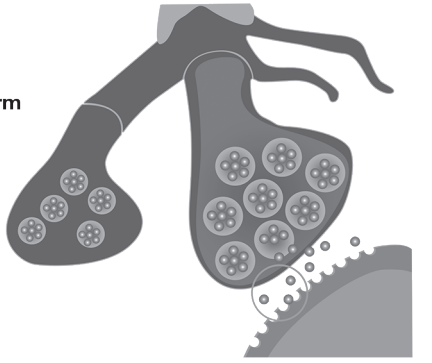
2a After injection the heamag-glutinine-toxin complex diffuses through the parenchyma by the toxin's heavy chain



2b The heavy chain induces a process of endocytosis. As a result the toxin is incorporated in the cytoplasm in a vesicle. The synaptic vesicles, containg acetylcholine, still function properly



2c After release into the cytosol the light chain binds to SNAP-25, which forms a blockage in the formation of the SNARE complex, preventing the secretion of acetylcholine



2d The effect of BoNT is overcome by collateral sprouting and restoration of function at the neuro-glandular junction (indicated by circle)

Figure 2 Mechanism of action for botulinum toxin A.

Since then, use of botulinum toxin for drooling has surged, and it is now generally considered the first-line treatment when conservative measures fail.

SURGERY

Although dismissed by some because of perceived risks associated with the procedures, surgery has been a mainstay in the treatment of drooling for several decades, and is regarded as one of the most effective treatments for severe drooling.

The first well-documented procedure was described by Wilkie in the mid-late 1960s, and consisted of bilateral relocation of the parotid duct to a more posterior position in the mouth (where secreted saliva could be more easily swallowed), coupled with excision of the submandibular glands. The procedure was reported to lead to a notable reduction of drooling in over 80% of patients, albeit with significant morbidity: in the largest published series of 123 patients, common complications included duct stenosis requiring additional surgical intervention (20%), transient parotid swelling (4%), dental or gingival problems (4%), xerostomia (2%) and wound dehiscence (2%).[30] Although studies on the Wilkie-procedure were published as late as 1990, the reported morbidity and technical complexity led several authors to propose modifications to Wilkie's technique; parotid duct ligation (rather than relocation) with excision of the submandibular glands was consequently reported to be similarly effective but with significantly less morbidity.[30-35]

Another procedure that attracted significant interest in the 1970s was surgical denervation of the major salivary glands. Denervation of the three major salivary glands is readily accomplished by sectioning the chorda tympani (for the submandibular and sublingual glands) and the tympanic nerve (for the parotid glands), both of which are readily accessible through a transtympanic approach. Success rates of 61-87% were reported, with limited morbidity and operative time[8,36-38], although some authors tried to further augment the result through simultaneous excision of a submandibular gland.[39] However, the inevitable loss of taste in the anterior two thirds of the tongue associated with section of the chorda tympani coupled with concerns over the long-term efficacy and the introduction of new techniques apparently led to a loss of interest in transtympanic neurectomy after 1980.[40] Some proponents have later argued that the reports of relapse were a result of sub-optimal interruption of the relevant nerves, and that more thorough section would lead to better results, but this was never scientifically confirmed.[41]

As interest in other techniques waned, bilateral submandibular duct relocation (SMDR) with or without excision of the sublingual gland arose as the de-facto standard surgical technique. The procedure was initially described in a Scandinavian article in 1969, and subsequently introduced in English literature by Ekedahl in 1974.[42,43] The procedure involves the rerouting of the submandibular ducts from the anterior oral cavity to the posterior oropharynx. As most drooling children have a dysfunctional oral phase of swallowing but a largely intact pharyngeal phase, the relocation of the ducts means that saliva is more easily swallowed while still preserving a physiologically humid oral cavity and allowing unimpaired parotid gland function for mastication. Routine resection of the sublingual glands was proposed by Crysdale to reduce ranula-formation, but this was not universally followed.[44] The high rates of success (approximately 80%) reported have led to the widespread adoption of this technique for anterior drooling.

More recently, duct ligation techniques have become the subject of increasing interest. First reported in 1999 by Klem and Mair, who performed ligation of all parotid and submandibular ducts to treat children with posterior drooling and recurrent pneumonias, several smaller case studies have been published that ligate one ore more parotid or submandibular ducts in various combinations.[14,45,46] The resulting reduction in overall flow facilitates saliva handling, and has been reported to improve both anterior and posterior drooling.

OBJECTIVES OF THIS THESIS

Despite the growing use of botulinum toxin, and the increasing body of evidence supporting surgery for drooling, there is a surprising lack of data comparing these (and other) treatments. Most intervention studies are uncontrolled, or feature controls from the same 'group' of interventions. This makes it difficult to estimate the effect of 'next line' treatments if other options fail.

Furthermore, there are still noticeable lacunae in the knowledge of individual treatments. With regards to botulinum toxin, for instance, there is little data on the efficacy of submandibular versus parotid versus combined injections, and there have been no systematic studies into the duration of its effect.

For surgery, there is a large amount of papers, but an unknown amount of 'evidence'. Many studies are experience reports, and their methodology has been criticized.[11]

This lack of knowledge has made the formation of a solid, evidence-based protocol for the management of drooling, difficult. This thesis therefore aims to provide further evidence for the various treatments drooling for drooling, as well as their relative merit, to support the development of such a protocol. Specific research questions include:

- How effective is submandibular duct relocation for severe drooling, and what is the quality of the associated evidence? (chapter 2).
- What is the effect of botulinum toxin for drooling when employed on a larger scale, and how long do its effects last? (chapter 3)
- Which factors influence outcomes of botulinum toxin when used for severe drooling? (chapter 4)
- What is the relative effect of submandibular vs. parotid injections of botulinum toxin? (chapter 5)
- What is the relative effect of botulinum toxin versus submandibular duct relocation (chapter 6)?
- What is the effect of salivary duct ligation for anterior and posterior drooling? (chapter 7)
- What is the relative value of botulinum toxin and surgery in the management of drooling? (all chapters)

A number of studies were completed to answer the research questions above. Chapter 2 explores the literature on submandibular duct relocation in a systematic review, to establish the effect and quality of the evidence for this surgical technique. Chapter 3 is large-scale prospective study of 131 children to establish the effect of botulinum toxin injected into the submandibular glands, using several outcome measures. As this study showed that over half of children show virtually no response to botulinum toxin, a subsequent study was performed to investigate factors that could influence botulinum toxin success. These results are presented in chapter 4.

Based on the fact that there is little data on the relative merits of parotid vs. submandibular injection of botulinum toxin, and the observation that some children appear to suffer more from parotid flow than submandibular flow, a small case study was performed to investigate the effect of submandibular botulinum toxin with parotid injection in a within-subjects settings. This study is described in chapter 5.

Chapter 6 presents a direct comparison of botulinum toxin versus submandibular duct relocation in a within-subjects analysis of patients who have undergone both treatments.

Chapter 7 is a case series of duct ligation for severe anterior and posterior drooling, and is presented as a first step for future research.

In the general discussion (chapter 8), the outcomes of the studies are discussed, and a potential evidence-based guideline for the management of drooling is proposed.

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Chapter 2

Submandibular duct relocation for drooling: a systematic review

SUMMARY

Objective: Drooling is an invalidating problem for children with neurological disorders. Many treatments have been described, but the level of evidence provided by relevant studies has been questioned. We performed a systematic review of the most common surgical procedure used to treat drooling in order to establish overall efficacy, morbidity and quality of the evidence.
Data Sources: Searches were performed on the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, PubMed and EMBASE in February 2013.
Study Selection: Titles and abstracts were reviewed, and the full text was retrieved of any article that potentially met eligibility criteria. The references of the retrieved articles were hand-searched for previously unfound studies.
Data Extraction: Relevant data regarding participants, interventions, outcome measures, follow-up duration, complications were extracted and entered into a database. All included studies were critically appraised using a validated checklist. Only studies with a score of at least 50% on the critical appraisal were considered for data synthesis.
Data Synthesis: Mean score for methodological quality was 38.4% (range: 21.4-67.9; SD 10.9). Three papers met the minimum methodological criteria set. Each described beneficial effects in >50% of patients. Meta-analysis of efficacy was not possible due to differences in outcome assessment. Complication rate was 8.7%. Most common were floor-of-mouth or tongue swelling (2.2%), post-operative hemorrhage (2.7%) and ranulas (3.2%).
Conclusions: Although there is a large amount of favorable experience with submandibular duct relocation, there is relatively little formal evidence for its efficacy. A more rigorous approach to evaluating this treatment, including control groups, blinding, and prospective, standardized outcome measures should be considered in future studies.

(**Submitted)**
Scheffer A.R.T., Jongerius P.H., van den Hoogen F.J.A.
Submandibulair duct relocation for drooling: a systematic review (submitted)

INTRODUCTION

Drooling is an often-underestimated clinical issue, mostly affecting people with neurological disorders.[1] Children with cerebral palsy are particularly frequently affected (estimated prevalence: 10-58%).[2] This leads to a broad spectrum of morbidity closely related to the underlying developmental problem. The lifelong physical and emotional consequences range from stigmatization, to severe invalidating drooling or even dehydration.

Although many treatments have been described, the management of drooling is complicated by a relative paucity of scientific evidence and comparative studies. Surgery appears to be considered the most effective –albeit most invasive- treatment for severe drooling, but even the most frequently studied procedure, bilateral submandibular duct relocation (SMDR) with or without excision of the sublingual gland, has been questioned with regard to scientific basis. Most reviews on the topic have generally been narrative in nature, on occasion noting that many studies 'lack scientific rigor'.3 We therefore performed a methodological review of studies describing submandibular duct relocation with or without sublingual duct excision with the primary objective of establishing the overall efficacy of this procedure, and the quality of the associated evidence.

METHODS

Our aim was to establish the overall efficacy and morbidity of submandibular duct relocation for drooling in people with neurological disability, and the corresponding quality of evidence. Primary outcomes were the reduction in drooling and major operative complications (defined as any event requiring surgical, endoscopic or radiological intervention, any life-threatening peri-operative complication requiring ICU-management, organ dysfunction or death). Secondary outcomes were xerostomia, caries and quality of life.

Search and selection

Eligibility criteria are shown in table 1. Searches were performed on the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, PubMed and EMBASE in February 2013. We used the following Mesh terms and keywords without language restrictions: (drool* OR dribbl* OR sialorrhea OR sialorrhea[MeSH]) AND (surger* OR surgi* OR rerou* OR reloc* OR sialodoch*). Titles and abstracts were reviewed, and the full text was retrieved of any article that potentially met eligibility criteria. References of retrieved articles were hand-searched for previously unfound studies.

Table 1 Study eligibility criteria

Target population	Patients with with non-progressive neurological disease AND invalidating drooling requiring surgical intervention, regardless of age, specific diagnosis, global motor function or intelligence
Intervention	Submandibular duct relocation with or without sublingual gland excision ONLY[a]
Outcome measure	ONE OR MORE OF: Extent of drooling (objective or subjective) Major complications Quality of Life Xerostomia Caries
Design	ONE OF THE FOLLOWING: Systematic review Randomized controlled trial Observational study with description of methodology, population and results.

[a] Studies combining SMDR or SMDR-SLGE with another intervention, eg. parotid duct ligation or neurectomy, without providing the results of duct relocation alone, were not considered.

Only studies that addressed one or more of the outcomes of interest in patients with non-progressive neurological disease were eligible for inclusion. Observational studies and case reports were also included, as long as they contained a section describing methods. Multiple reports of the same study were linked together. For studies describing parts of the same population over a longer period of time, the most complete study was used.

Critical appraisal

Included studies were critically appraised using the checklist developed by Downs and Black, which allows the appraisal of both randomized and non-randomized intervention studies.[4] This 27-item questionnaire addresses quality of reporting, external validity, internal validity (bias and confounding) and power. As initial search showed there were little or no studies with control groups, the last item on the questionnaire (regarding power), was not used. The maximum achievable score was therefore 28 points.

Data collection and analysis

A standardized set of data was extracted from each included study and entered into a database. If essential information couldn't be established from a study, an attempt was made to contact the original authors.

In order for a study to be included in outcome analysis, we set two specific criteria regarding methodological quality. Firstly, only studies that scored at least 14 points (out of 28) on the critical appraisal qualified as articles with acceptable methodology. Secondly, for efficacy-analysis, we required studies to prospectively assess outcome through systematic repeated measurements, both pre- and post-operatively; the subjective nature of drooling can make its quantification difficult, and we therefore judged that the mere use of 'outcome scales' (eg: 'improved', 'not improved', 'worse') without formal pre-operative evaluation carried too great a risk for bias.

No distinction was made between submandibular duct relocation and submandibular duct relocation with excision of the sublingual glands, based on the assumption that the two interventions are so similar that there would not be a meaningful difference in efficacy. The sublingual glands are responsible for less than 5% of resting saliva production, and the addition of sublingual gland excision is only intended to reduce the risk of ranula formation.

RESULTS

Fifty-nine potentially relevant papers were initially identified based on title and abstract. Seven were not available in full-text in any library nationwide. The remaining 52 were retrieved and analyzed. 16 did not meet eligibility criteria (12 for not describing methods, 3 for describing another intervention and 1 for not addressing relevant outcomes). Studies describing (parts of) the same population with the same outcomes were pooled. This left 25 studies, all observational in nature (figure 1), describing 24 populations (one study addressed efficacy and caries formation in the same population in two different papers).[5-29]. Characteristics of all studies are shown in table 2.

The average overall score of the critical appraisal was 38.4% (range: 21.4-67.9; SD 10.9). The mean score for reporting was 48.7% (range 27.3-81.8; SD 14.5%), for external validity 54.7% (range 0-100; SD 28.9%), for bias 39.4% (range 14.3-71.4; SD 9.2) and for confounding 14.3% (range: 0-42.9; SD 9.2). The especially low mean score for confounding was a result of the fact that only 6 studies used any form of control group to compare outcomes; the other studies automatically scored '0' on items relating to controls.

No study performed random allocation or blinding of either patients or outcome assessors. Of the 6 studies that described multiple treatments in the same study, only three described the method of treatment allocation. In 9 cases, it was unclear

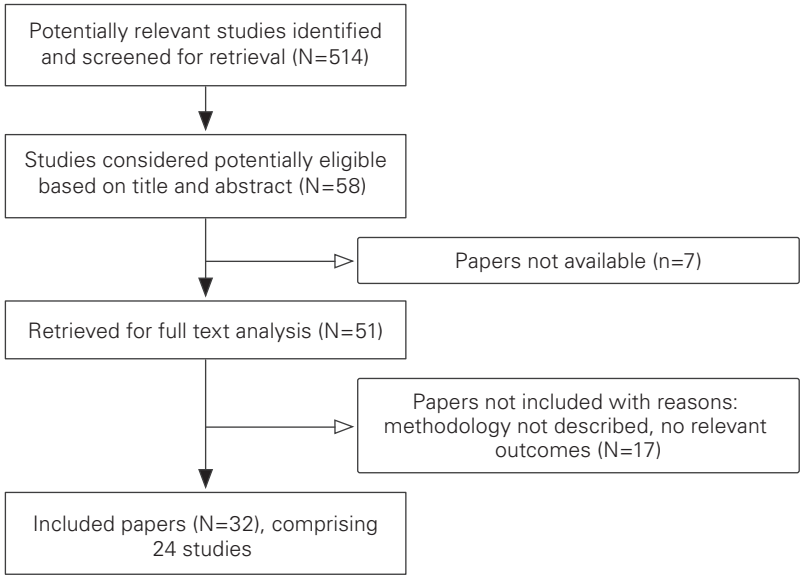

Figure 1 QUORUM flow chart for study selection.

how patients were selected to participate in the study, and only two studies provided both inclusion criteria and exclusion criteria.

Primary outcomes

Outcomes are summarized in table 3. Three studies describing efficacy or major complications met the minimum methodological requirements. Mean overall score on the critical appraisal for these studies was 61.6% (range: 50.0-71.4; SD 9.8). Unfortunately, the heterogeneity in outcome assessment made meta-analysis for efficacy impossible. Each study will therefore be described separately.

Ekedahl performed a prospective, uncontrolled study of submandibular duct relocation without sublingual gland excision in 11 patients with brain damage aged 7-41 years.[6] Patients were evaluated prior to surgery and 1 year after. Objective assessment through the collection of radioactively labeled saliva at 30-minute intervals showed a 64% average reduction in dribbled saliva compared to pre-operative levels, with 9 out of 11 patients (82%) demonstrating a statistically significant improvement (paired t-test; $P \leq 0.05$). Subjective assessment was performed in various settings (at rest, at mealtime and in an engaged situation)

by 3 team members on a 4-point scale. Six patients (55%) were judged to have improved subjectively, 4 (36%) had no benefit, and 1 had deteriorated. Post-operative scintigraphy of the submandibular glands suggested unimpaired salivary gland function in all patients.

Greensmith et al. published an uncontrolled prospective analysis of submandibular duct relocation with sublingual gland excision (SMDR-SLGE) in 72 neurologically damaged patients between 4-19 years.[21] The authors were contacted successfully for additional information regarding the study. Outcome assessment was primarily based on the DS/DF-scale, which expresses drooling severity (DS) on a scale from 1-5 (1, 'no drooling'; 5, severe, invalidating drooling') and drooling frequency (DF) on a scale from 1-4 (1, 'never drools'; 4, 'always drools').[8] Both clinicians and caretakers scored children preoperatively and 2 and 5 years postoperatively. The number of daily-required bibs and a caretaker VAS-score were also recorded. The median preoperative drooling severity (DS) was 4.8 and the median preoperative drooling frequency (DF) 4.0. After 2 years the median DS was 3.0 (–1.8; $P < 0.001$) and the median DF 2.8 (–1.2; $P < 0.001$). 78% of patients experienced a reduction ≥1 in drooling severity and 58% in drooling frequency. The median number of bibs required had fallen from 4 to 0 ($P < 0.001$), and the median reduction in VAS-score reported by parents was 75%. Follow-up at 5 years was incomplete (57%), but showed similar results: DS 3.0 ($p<0.001$; reduction ≥1 in 66%), DF 3.0 ($p<0.001$; reduction ≥1 in 66%), median number of bibs: 1. 10% of patients required additional surgery in the form of parotid duct ligation to achieve a satisfactory result. These children were not reported separately.

Glynn et al. performed a prospective comparison between SMDR and SMDR-SLGE in 100 patients between 4-19 years, mostly with cerebral palsy.[23] Patients were included successively and parts of the results were published in an earlier study. The primary outcome was a caretaker VAS (scale 1-10), evaluated pre-operatively, 4 months post-operatively and at the end of follow-up (> 12 months). The outcomes were reported stratified by pre-operative scores. The mean pre-operative VAS in the SMDR-group was 8.9. Patients with a pre-operative score of 10 had a mean post-operative score of 2.3, those with 9 of 1.4, those with 8 of 2.7 and those with 7 of 2. In the SMDR-SLGE-group the mean pre-operative score was 9.1 and outcome reductions per pre-operative score were: from 10 to 2.3, from 9 to 2.8, from 8 to 2.2, and from 7 to 2. Analysis of co-variance demonstrated no statistically significant difference in efficacy between the two interventions ($P = 0.643$).

The final study was conducted in our centre.[29] A historic cohort was formed of 19 people with cerebral palsy from 6-23 years with severe drooling who underwent

Table 2 Characteristics of included studies

Group	Paper	Study characteristics			
		Design	Sample size	Intervention	Control
1a	Ericson 1973	Observational	10	SMDR	none
1b	Ekedahl 1974	Observational	11	SMDR	none
2	Cranin 1982	Observational	5	SMDR	none
3	Fear 1988	Observational	8	SMDR	none
4	Shott 1989*	Observational		SMDR, SMDR-BTN[1]	none[2]
5	Arnrup 1990	Observational	17	SMDR	none
6	Burton 1991	Observational	20	SMDR	none
7	Hotaling 1992	Observational	6	SMDR-SLGE	
8	Ethunandan 1998	Observational	20	SMDR-SLGE	none
9	Mankarious 1999	Observational	75[3]	SMDR	none
10	Wilson 1999	Observational	71	SMDR, SMDR+PDL, USMDR, SMDR+Wilkie, SMDR+reversal Wilkie [5]	none[2]

Study characteristics		Critical appraisal				
Main Outcome	Main findings	Reporting	External validity	Bias	Con-founding	Total
Caries	4 children increased caries lesions, 1 decreased	64%	33%	71%	29%	54%
Objective and subjective drooling	64% mean reduction objective amount of drooled saliva. 6 children subjectively improved, 1 worsened, 5 unchanged	55%	100%	71%	29%	57%
Subjective drooling improvement	3 excellent result, 2 good, 1 fair	36%	67%	57%	14%	39%
Clinical judgment	6 children improved, 2 unimproved	36%	100%	29%	14%	36%
Parent questionnaire	Zero of 6 children in SMDR-group improved, 5 of 20 in SMDR-BTN group	45%	33%	43%	14%	36%
Caries	High prevalence of caries compared to earlier epidemiological study in healthy Swedish children	82%	67%	57%	14%	57%
Subjective drooling improvement	100% short-term improvement. 85% still improved at end of follow-up. Additional neurectomy required in 10%	45%	67%	29%	14%	36%
		55%	33%	43%	29%	43%
Subjective drooling improvement (caretaker and clinician)	Clinician: 55% much better, 40% better, 5% no change. Caretakers: 84% significantly improved: 84%, 16% not improved.	55%	67%	29%	14%	39%
Subjective drooling improvement	Short term (<3 months): 61% much better, 21.3% better, 14.7% unchanged, 2,7% worse. Long term: 50.8% much better, 28.8% better, 20.3% unchanged, 0% worse.	55%	67%	43%	29%	46%
Subjective drooling improvement	SMDR: 6 excellent, 6 good, 4 fair, 0 poor. SMDR+PDL: 23 excellent, 24 good, 1 fair, 1 poor. USMDR: 2 excellent, 2 good, 0 fair, 0 poor. SMDR+Wilkie: 1 good. SMDR+reversal Wilkie: 1 good	36%	33%	29%	0%	25%

Table 2 Continued

Group	Paper	Study characteristics			
		Design	Sample size	Intervention	Control
11	Panarese 2001	Observational	35	SMDR	none
12	Crysdale 2001	Observational	475	SMDR	SMDR-SLGE
13	Walker 2001	Observational	35	SMDR-SLGE[4]	none
14	De 2003	Observational	56	SMDR, SMDR-SLGE	none
15	Uppal 2003	Observational	23	SMDR-SLGE	none
16	Greensmith 2005	Observational	72	SMDR-SLGE	none
17	McAloney 2005	Observational	21	SMDR-SLGE	none
18	Glynn 2007	Observational	100	SMDR	SMDR-SLGE
19	Puraviappian 2007	Observational	8	SMDR-SLGE	none
20	Syeda 2007	Observational	9	SMDR, USMDR[5]	none

Study characteristics		Critical appraisal				
Main Outcome	Main findings	Reporting	External validity	Bias	Con-founding	Total
Subjective drooling improvement	Short term (3mths): 82.4% improved. Long term: 76.5% improved.	55%	33%	14%	14%	32%
DS/DF rating scale (range: 2-9)	SMDR (n=115): Pre-op score 8.2. Post-op: 4.8. SMDR-SLGE (n=106): Pre-op 8.1. Post-op 4.9.	45%	33%	43%	29%	39%
Rating scale (drooling severity+ frequency; range 0-8) pre-op vs post-op	Drooling score reduced from pre- operative mean of 7.3 to a post-operative mean of 2.3	36%	100%	29%	29%	39%
DS/DF rating scale	Pre-op mean DF 3.7, mean DS 4.1. Post-op mean DF 1.7, mean DS 1.9	27%	67%	14%	14%	25%
Subjective drooling improvement	13 excellent, 3 good, 4 fair, 3 poor	36%	67%	29%	14%	32%
DS/DF rating scale	After 2 years (n=67): Med. reduction DF from 4.0 to 2.9 (P<0.001). >1 reduction in 58%. DS 4.8 to 3.0 (p<0.001), >1 reduction in 78%.	64%	100%	57%	14%	54%
Subjective drooling improvement (various outcome scales)	Pre-op: 1 dry-mild drooling, 1 mild-moderate, 7 moderate-severe, 12 severe-profuse. Postop 9, 4, 5, and 3 children, respectively.	45%	33%	29%	14%	32%
VAS (1-10)	SMDR (n=71): average reduction 10->2.3. 9->1.4 8->2.7 7->1. SMDR-SLGE (n=29): avg reduction 10->2, 9->2.8, 8->2.2, 7->2.	82%	67%	71%	57%	69%
VAS (1-10)	87.5% 'significant reduction' (from score ≥7 before surgery to ≤2 afterwards)	27%	0%	57%	29%	32%
Glasgow Children's Benefit Inventory (-100 – 100)	Average improvement +33.	55%	67%	29%	14%	39%

Table 2 Continued

Group	Paper	Study characteristics			
		Design	Sample size	Intervention	Control
21	Stamataki 2008	Observational	33	SMDR-SLGE, SGE+PDL, 4DL	none[2]
22	Katona 2008	Observational	14	SMDR, SMDR-SLGE	none
23	Copley 2008	Observational	32	SMDR, SMDR-SLGE	none
24	Scheffer 2010	Observational	19	SMDR-SLGE	botulinum toxin

1 Submandibular duct relocation with bilateral tympanic neurectomy and unilateral chorda tympani ligation
2 Study described multiple interventions, but since there was no clear method for allocation this was judged not to be a true 'control' group
3 78 Patients in original sample. Short-term data available for 75 patients, long-term for 59 patients.
4 29 patients bilateral SMDR. 4 patients unilateral due to earlier surgery.
5 5 patients bilateral SMDR, 4 patients unilateral SMDR
6 Numerous patients still on anticholinergic drugs post-op: SMDR-SLGE 33%, SMDR+PDL 21%, 4DL 54%. Additional interventions also required in some patients in all groups

Abbreviations: SMDR, (bilateral) submandibular duct relocation; USMDR, unilateral submandibular duct relocation; SLGE, sublingual gland excision; SGE: submandibular gland excision; PDL, parotid duct ligation; 4DL, 4-duct ligation; DS, drooling severity; DF, drooling frequency

Study characteristics		Critical appraisal				
Main Outcome	Main findings	Reporting	External validity	Bias	Con-founding	Total
Parent questionnaire	SMDR-SLGE (n=6): 83% happy or moderately happy. SMDR+PDL (n=14): 79% happy-moderately happy. 4DL (n=13): 30% happy-moderately happy[6]	45%	33%	14%	29%	32%
Subjective drooling improvement	4 excellent,4 good, 3 fair, 3 poor	55%	67%	29%	14%	39%
Subjective drooling improvement	Short-term 78% 'marked improvement', 22% 'little improvement' (n=23). Long-term (n=10): 50% 'dry', 30% 'somewhat wet', 20% 'still very wet'	36%	0%	29%	0%	21%
Drooling Quotient (DQ; 0-100)	Measured 8 and 32 weeks after surgery, the DQ fell to 10 and 4, respectively, from a baseline value of 28 (P<0.001). Signficant difference in favour of SMDR vs botulinum toxin efficacy.	91%	33%	71%	57%	71%

Table 3 Evidence table summarizing primary and secondary outcomes

	Quality assessment						Summary of Findings	
No of studies (# of participants)	**Design**	**Limitations**	**Consistency**	**Directness**	**Precision**	**Other Considerations**	**Absolute Effect**	**Quality of evidence**
Primary Outcomes								
Drooling (follow-up 2-60 months)								
4 (202)	Observational	serious (–1)[a]	No serious inconsistency	Direct	No serious imprecision	Strong association (+1)[b]	see text	++00, LOW
Major Complications (follow up 4-60 months; outcome in 'incidence')								
3 (183)	Observational	No serious limitations	No serious inconsistency	Direct	No serious imprecision	-	16 (8.7%)	++00, LOW
Secondary Outcomes								
Xerostomia (follow-up 9-60 months; outcome in 'incidence')								
1 (17)	Observational	serious (–1)[c]	No serious inconsistency	Direct	Imprecision (–1)	-	0 (0%)	+000, VERY LOW
Dental Caries (follow-up 12-218 months)								
2 (27)	Observational	serious (–1)[a]	No serious inconsistency	Direct	No serious imprecision	-	see text	+000, VERY LOW
Quality of Life (follow-up 0.6-5.9 years; outcome in 'Glasgow Benefit Inventory Score; better indicated by higher score)								
1 (9)	Observational	serious (–1)[a]	No serious inconsistency	Direct	No serious imprecision	-	+33.0	+000, VERY LOW

[a] Limitations include lack of formal control groups or randomization, blinding of outcome assessors and contamination of intervention group

[b] 55% or more participants showing notable clinical improvement or satisfied with outcome in all studies

[c] No apparent clear, consistent definition of 'xerostomia'

injections with botulinum toxin, followed by submandibular duct relocation at least 6 months later. Although data was collected prospectively, the study group was formed retrospectively. The primary outcome was the direct-observational drooling quotient (DQ). From a baseline value of 28, submandibular duct relocation led to a reduction in DQ to 10 after 8 weeks, and 4 after 32 weeks ($p<0.001$). Duct relocation was found to be significantly more effective than botulinum toxin ($p<0.0001$).

Major complications in these studies occurred in 8.4% of children (over 202 patients; range 5.3%-9.7%). Complications are listed in table 4.

Floor-of-mouth or tongue swelling with transitory respiratory problems was reported in 6 patients (3.0%), major post-operative hemorrhage in 5 (2.5%). Ranulas requiring surgical excision were reported six times (3.0%), and only in patients who did not undergo sublingual gland excision. Excluding patients who underwent sublingual gland excision, the overall incidence of ranulas was 7.2%.

Secondary outcomes

Only a single study that our methodological criteria explicitly reported the incidence of xerostomia, which was reported to be 0% in 17 patients.[10]

Caries was addressed in two studies that met the methodological criteria. Ericson evaluated 10 children both pre-operatively and 1 year post-operatively.[5] Increases of early caries lesions were seen in 4 children. 9 children showed an increase in decayed, missing or filled surfaces (DMFT) and 10 in decayed, missing or filled teeth (DMFS), although the authors noted that only two children had caries activity higher than average in their age groups. Arnrup analyzed 17 children after a mean of 9.2 years (range 1-18) and found a similar prevalence of overall caries compared to an earlier epidemiological study (DMFS: 10.7 vs. 11.9). 10 High DMFS scores were, however, recorded in the mandibular incisal and canine area (teeth 33-43; 25% versus 0.2% in the aforementioned epidemiological study), which suggests the diversion of salivary flow to the posterior oral cavity has consequences for the anterior dentition.[10]

Quality of life was addressed in a case series of nine children, which used the Glasgow Benefit Inventory to retrospectively address the impact of bilateral (n=5) and unilateral (n=4) submandibular duct relocation.[25] Uncharacteristically for this procedure, the authors reported only 2 children suffered from cerebral palsy, developmental delay or motor disorder. After a mean follow-up of 4 years, the mean improvement on this scale was 33.0 (range: -16.6-66,66; SD 30.3). This study did not meet our methodological criteria (critical appraisal score: 39%).

Technical variations

Excision of the sublingual duct (SLGE) is the most important technical variation on submandibular duct relocation. This procedure is performed during initial surgery to avoid ranulas, which would otherwise occur in approximately 7% of patients.

The single study that directly compared SMDR with SMDR-SLGE found a statistically significant increase in both operative time and hospital stay: sublingual gland excision lead to a mean increase in operative time from 30 to 55 minutes (P = 0.001) and lengthened hospital stay from 4 to 5.8 days (P = 0.001).[23] The same study also found a non-significant increase in post-operative hemorrhage following SMDR-SLGE (13.7% vs. 3.0%; 95%-CI 0.95-32.1), and stated that parents appeared more concerned about post-operative pain following SMDR-SLGE (36% vs. 12%).

DISCUSSION

Although submandibular duct relocation is likely the most frequently employed surgical procedure to treat drooling, there is relatively little formal evidence for its efficacy. Most papers appear to be 'expert reports' rather than systematic studies, with varying levels of scientific quality, and a wide variety of outcome measures.

Clinical experience with the procedure is clearly favourable, judging from the fact that the studies retrieved for this review described well over 1000 patients and nearly every included study reported success rates of well over 50% - albeit with widely varying definitions of 'success'. The physiological principles underlying the procedure are attractive, by not reducing the salivary flow but by redirecting it to a position where it is more easily managed by individuals with a (partially) dysfunctional oral phase of swallowing. Post-operative scintigraphic assessment in a number of studies imply that the submandibular glands continue to function normally in the majority of patients.

Most authors report that the procedure is well-tolerated, though our review suggests that post-operative hemorrhagic complications leading to airway obstruction can be a rare but serious complication that might warrant strict post-operative observation. The addition of sublingual gland excision appears to protect against ranulas in 7.2% of children, but potentially leads to more major perioperative complications.[23]

The available data makes it difficult to determine the value of submandibular duct relocation, and especially its efficacy and morbidity compared to other surgical and nonsurgical treatments.

A 2009 study made an impressive attempt to compare various surgical procedures for drooling in a meta-analysis of all studies describing any surgical intervention for drooling, regardless of methodology, by reducing outcome scales to 'improved' or 'not improved'.[30] Useful as such an approach is, the reduction of such widely varying outcome measures to a subjective dichotomous scale would appear troublesome. Also, this approach does not quantify the size of the effect, and does not reflect that a full improvement in drooling might have a particularly poor side effect in the form of xerostomia.[17]

It appears the wider adoption of well-established evidence-based medicine guidelines in the research of drooling would significantly facilitate such meta-analysis in the future. Ideally, research would mostly be in the form of well-designed randomized controlled trials, or rigorous prospective observational studies.[31] In these cases, a number of simple measures could notably improve the validity and comparability of nearly all studies: a control group to provide a measure of comparison, blinding of outcome assessors to reduce experimenter's bias, and prospective, standardized follow-up of both subjective and objective treatment outcome.

The treatment of drooling has long been subject to debate, with various experts strongly preferring one approach to another. Especially as new treatments such as botulinum toxin and salivary duct ligation are increasingly adopted, a randomized controlled setting, standardized outcomes, detailed descriptions of the patient population under study and systematic evaluation of side-effects are essential in future studies if 'expert opinion' is to be substituted for a more evidence-based consensus. As the problem itself, the management of drooling is multifaceted and complex. Only rigorous research can assure optimal treatment plans for this vulnerable population in the future.

Conclusion

There is low quality evidence that submandibular duct relocation is effective in the treatment of drooling for neurologically handicapped patients.

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Chapter 3

Efficacy and Duration of Botulinum Toxin Treatment for Drooling in 131 Children

SUMMARY

Objective: To address the efficacy of botulinum toxin and the duration of its effect when used on a large scale for the treatment of drooling in children with neurological disorders.
Design: Prospective cohort study.
Setting: Academic multidisciplinary drooling clinic.
Patients: A total of 131 children diagnosed as having cerebral palsy or another nonprogressive neurological disorder and who also have moderate to severe drooling.
Intervention: Injection of botulinum toxin to the submandibular glands.
Main Outcomes: Direct observational drooling quotient (DQ) (0-100) and caretaker visual analog scale (VAS) scores (0-100).
Results: A clinically notable response was found in 46.6% of children, reflected in a significant mean reduction in DQ from a baseline of 29 to 15 after 8 weeks and 19 after 32 weeks (P < .001). The mean VAS score decreased from 80 at baseline to 53 after 8 weeks and increased to 66 after 32 weeks (P < . 001). Kaplan-Meier analysis showed that patients who initially responded to treatment experienced relapse after a median of 22 weeks (interquartile range, 20-33 weeks).
Conclusions: Our study provides further support for botulinum toxin's efficacy for treatment of drooling in approximately half of patients for a median of 22 weeks. Further optimization of patient selection should be an area of attention in future studies.

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INTRODUCTION

Drooling is a common problem for children with neurological disorders. Recent estimates suggest a prevalence of nearly 60% in children in special care school, of which 33% could be classified as severe.[1] Drooling in these children is usually caused by a combination of low oral sensitivity, infrequent swallowing, poor posture and mental ability, and dysfunctional oral motor control leading to excessive pooling of saliva in the anterior oral cavity and consequently to unintentional saliva loss.[2,3] Hypersalivation might only be an issue in children with dyskinesia as a result of hyperkinetic oral movements.[4]

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Non-progressive congenital neurological disease	Known hypersensitivity to botulinum toxin or any part of the formulation
Invalidating drooling (TDS[a] ≥ 3).	Missing baseline measurement, or missing >1 follow-up measurement.
Conservative measures have not led to notable reduction in drooling, or are not feasible (eg. due to low developmental level)	Known use of other agents that influence drooling during the treatment
	Progressive disease

[a] Teacher drooling scale; a TDS of 3 corresponds with "occasional drooling, intermittent throughout the day"

The morbidity associated with sialorrhea has long been established in the literature.[5-8] Depending on the associated neurological disorder, cognitive abilities, and oral motor function, affected children may experience anything from stigmatization and social neglect to numerous daily clothing changes, perioral dermatitis, aspiration pneumonia, or even dehydration. The management of drooling has long been a matter of debate. Speech therapy and behavioral therapy have been proposed, but our clinical experience suggests that this is only useful in children with sufficient cognitive abilities to train.[9] Treatment with systemic anticholinergics appears to be effective, but these drugs are associated with notable adverse effects.[10] Various surgical techniques have been reported to be highly effective, but owing to their invasive and often irreversible nature, other treatment techniques should be attempted first.

Intraglandular botulinum toxin, therefore, offered a promising treatment option when first suggested a decade ago.[11] Its localized nature and strong anticholinergic properties offered the potential to reduce drooling without the invasiveness of surgery. The intervention was subsequently demonstrated to be effective in a large

number of studies, with most authors finding a clinically significant reduction in unwanted saliva loss in 33% to 64% of patients for approximately 2 to 6 months.[12] Botulinum toxin has been in use in our multidisciplinary drooling clinic since 1999. Our group has previously reported our initial results elsewhere.[13-15] Our present aim is to report on the efficacy and duration of effect of botulinum toxin when used on a larger scale in clinical practice.

METHODS

Participants

Children eligible for inclusion were diagnosed as having cerebral palsy or another nonprogressive neurological disorder and were seen in our multidisciplinary drooling clinic for moderate to severe drooling. For each patient, conservative measures had not had sufficient effect or were not feasible, and injection of botulinum toxin to the submandibular glands was recommended as treatment. Full inclusion and exclusion criteria, including Teacher Drooling Scale[16], are listed in Table 1.

Study design

Patients were enrolled consecutively between January 2000 and July 2008. Assessment of the severity of drooling took place under standardized conditions before treatment and 8 and 32 weeks after treatment. This allowed for a within-subjects design in which the patient's baseline condition was used as a reference to evaluate the effects of injection over time.

Procedures

For the injection of botulinum toxin, children were under general anesthesia. A single dose of botulinum toxin type A (Botox; Allergan, Nieuwegein, the Netherlands), reconstituted with 0.9% sodium chloride, was then injected into the submandibular glands using a 25-gauge needle and a 1-mL syringe. The 1-mL volume was chosen to allow the dose to be fractionated over at least 3 sites in the gland while minimizing the risk of diffusion into surrounding tissues. We used 15 U of botulinum toxin per gland for children weighing less than 15 kg, 20 U/gland for children weighing between 15 kg and 25 kg, and 25 U/gland for children weighing more than 25 kg. During injection, the dose was fractionated over at least 3 sites in the gland under ultrasonographic guidance. The sublingual glands and parotid glands were not treated.

Outcome measures

The drooling quotient (DQ), a validated, direct-observational semiquantitative method to assess the severity of drooling served as the primary outcome measure for both efficacy and duration of effect.[14] The DQ was defined as the percentage of time the patient drooled and was measured by 1 of 2 specially trained speech language therapists. During two 10-minute sessions (one while the patient was concentrating and the other while the patient was distracted), the absence or presence of new saliva on the lip was recorded every 15 seconds for a total of 40 observations per session. Patients were evaluated in the morning, at least 1 hour after a meal, while they were awake and sitting upright. Response to treatment was defined as a 50% reduction in DQ from the baseline value.

A caretaker visual analog scale (VAS) score reflecting the severity of drooling over the previous 2 weeks served as secondary outcome measure. Caretakers marked the extent of drooling on a 10-cm line following specific instruction. The VAS score was obtained by measuring the position of the mark in millimeters from the right end of the scale on a scale from 0 to 100, with 100 corresponding to severe drooling. A reduction of 2 SDs from the baseline VAS score was considered clinically significant.

Finally, qualitative assessments were made throughout the study of oral hygiene (including xerostomia), saliva viscosity, feeding behavior, and speech.

Statistical analysis

Statistical analyses were performed using SPSS software, version 16.0.2.1 for Mac OS X (SPSS Inc, Chicago, Illinois). For analysis of the DQ and VAS score, we used descriptive statistics; conducted paired t tests to assess differences of paired observations; performed independent t tests and linear regression to compare groups; and performed a multivariate analysis of variance with a repeated measures design to evaluate the treatment response pattern over time, using a within-subjects design with the measurement moments as the variables. Missing follow-up data were adjusted in 2 ways: (1) by carrying the last observation forward (CLOF) and (2) through a worst-case scenario (WCS). In the CLOF procedure, missing data were replaced with the last previous observation; in the WCS procedure they were replaced by baseline values, thus introducing a bias toward the null. The outcomes of both approaches are presented herein.

Analysis of the duration of the effect of botulinum toxin injection was accomplished by observing patients who were classified as responders beginning 8 weeks after intervention and performing a time-to-event (Kaplan-Meier) analysis until relapse

occurred. The interval between the last known date of success and the end date was halved to compensate for the gradual loss of effect associated with botulinum toxin. All tests of significance were 2 sided, and $P \leq .05$ was considered statistically significant.

RESULTS

A total of 133 children were initially included. One was subsequently excluded because of a missing baseline assessment, and another for a complete lack of follow-up data. This left 131 children suitable for analysis, 77 boys and 54 girls. The mean (SD) age at the time of treatment in this group was 10.9 (4.7) years (age range, 3-27 years). Most of the patients were diagnosed as having cerebral palsy (90.1%), while the others had psychomotor retardation of unknown origin. Over half of the children had a Gross Motor Function Classification System score of 4 or higher, indicating that they relied on a wheelchair for mobility. A total of 41.2% of them had well-controlled epilepsy, and another 14.5% had intractable epilepsy.

Primary outcomes

The follow-up rate at the 2-month interval (median interval, 8 weeks; interquartile range [IQR], 8-9 weeks) was 97.8%, and at the 8-month interval (median interval, 32 weeks; IQR, 31-34 weeks) it was 94.0%. No evidence was found of selective loss of follow-up.

Analysis of the DQ was first performed on the data adjusted by CLOF. Repeated measures analysis showed a highly significant reduction (Hotelling Trace $F = 38\,360$, $P < .001$), depicted in Figure 1. At the first follow-up, the mean DQ had fallen from a baseline value of 28.8 to 15.5, a change of –13.3 ($P < .001$). Sixty-one patients experience a 50% reduction in DQ from baseline and so were considered "responders" by our definition. Although follow-up after 32 weeks showed the beginning of a return to baseline, there was still a significant difference compared with the baseline assessment (–10.0) ($P < .001$). As a result of the high follow-up rate, WCS analysis did not yield notably different results ($F = 38\,878$, $P < .001$). Patient sex ($P = .10$), neurological score ($P = .07$), or age ($P = .32$) did not significantly influence outcome.

Detailed time-to-event analysis was subsequently performed for the 61 responders at the 2-month follow-up to investigate the duration of the effect provided by botulinum toxin. Disease-free survival was defined as the time the DQ remained below 50% of baseline values, and no repeated intervention was indicated or

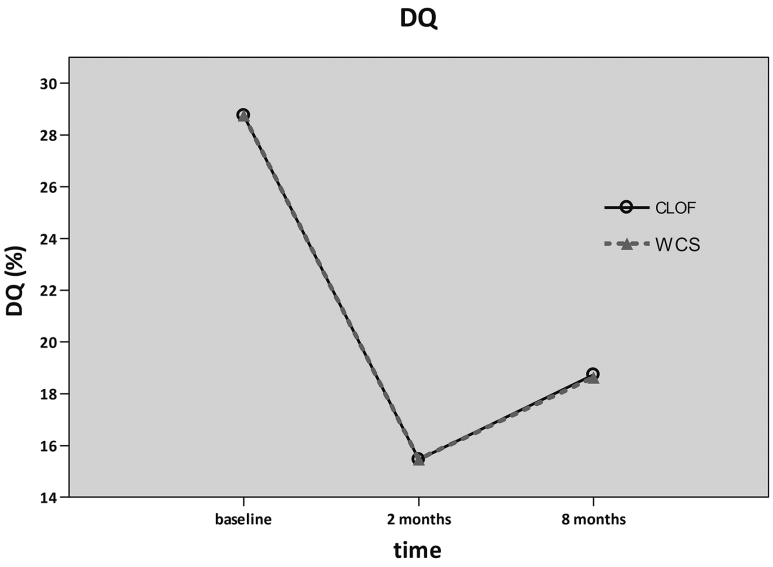

Figure 1 Mean direct observational drooling quotient (DQ) for the study patients (n = 131). From a mean baseline of 28.7, the DQ showed a significant reduction to 15.5 after 8 weeks and 18.7 after 32 weeks (P < .001).

performed. Kaplan-Meier analysis showed a median duration of effect of 150 days (22 weeks) (Figure 2). An IQR of 138 to 235 days (20-34 weeks) indicated that 75% of patients who initially responded well to therapy stopped demonstrating a clinically significant effect before 32 weeks after injection. Four patients were lost to follow-up before relapse could be established (right-censored observations). At the last observation, these patients still experienced an ongoing effect, and the duration of effect in these cases is thus not known.

Secondary outcomes

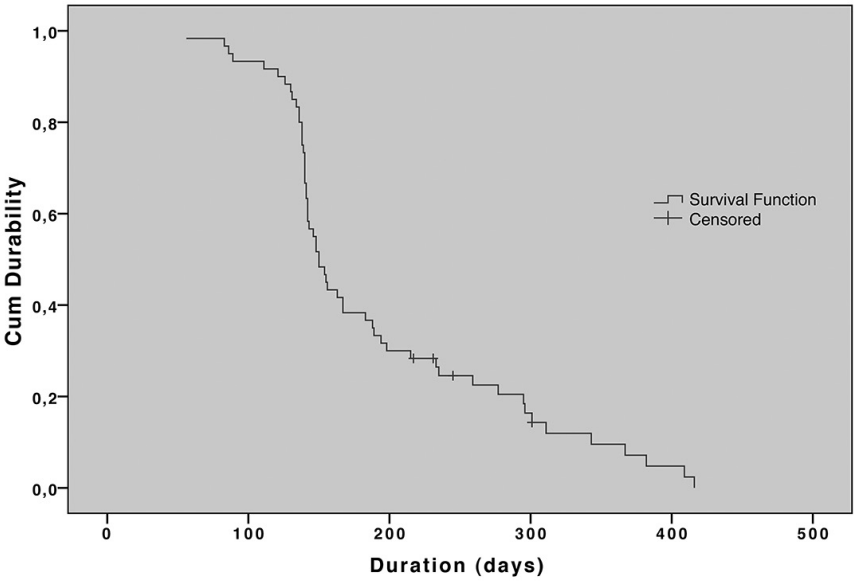

Figure 2 Duration of botulinum toxin effect. Kaplan-Meier analysis of longevity of botulinum toxin injection effect in patients who showed a response to treatment after 8 weeks (n = 61). The median duration was 150 days; interquartile range, 138 to 235 days.

For 3 patients, VAS scores could not be analyzed owing to a missing baseline score. Analysis of the remaining 128 children showed a significant pattern similar to the DQ ($F = 58\,804$, $P < .001$), which is depicted in Figure 3. After 8 weeks, the mean VAS score had fallen from a baseline value of 80.4 to 53.9 ($P < .001$). After 32 weeks, the VAS score had risen to 65.7 ($P < .001$) (Table 2). Although there were more missing VAS score values (6 after 8 weeks, 20 after 32 weeks) than DQs, no meaningful differences were found between the CLOF and WCS analyses; only the 32-week score was slightly higher in the WCS setup (68.8). Response rates, defined as a reduction of 2 SD from the baseline score, were 51.0% after 8 weeks and 26.0% after 32 weeks.

Although injections were usually well tolerated, there were several minor adverse effects in this series. Changes in the viscosity of saliva were perhaps the most common side effect of treatment: 54 children experienced thickening of saliva at

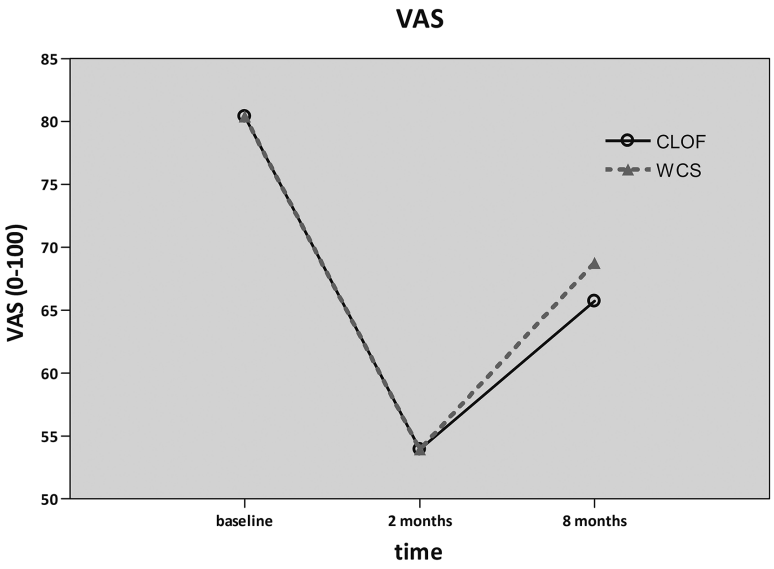

Figure 3 Mean visual analog scale (VAS) scores for the study patients (n = 128). From a mean baseline value of 80.4, the VAS score fell to 53.9 after 2 months (P < .001). Although it had increased by 8 months, there was still a significant effect compared with baseline (CLOF, 65.7; WCS, 68.7) (P < .001). CLOF indicates carry last observation forward; WCS, worst-case scenario.

Table 2 Mean differences between baseline and follow-up measurements

	DQ (95%-CI)		VAS (95%-CI)	
Observation Period	**CLOF**	**WCS**	**CLOF**	**WCS**
Baseline to 2 months	-13.3 (-16.3 – -10.3)	-13.3 (-16.3 – -10.3)	-26.5 (-31.3 – -21.6)	-26.5 (-31.3 – -21.6)
Baseline to 8 months	-10.0 (-13.0 – -7.0)	-10.1 (-13.1 – -7.2)	-14.7 (-19.1 – -10.3)	-11.6 (-15.6 – -7.7)
2 months to 8 months	3.3 (0.8 – 5.7)	3.2 (0.7 – 5.7)	11.8 (7.3 – 16.3)	14.8 (9.9 – 19.7)

Abbreviations: CI, confidence interval; DQ, drooling quotient; CLOF, carry last observation forward; WCS, worst-case scenario.

[a]Based on paired-samples t-tests, 2-sided P ≤ 0.05.

some point as noticed by parents or detected by clinicians at follow-up (41.2%). Interestingly, a reduction in saliva viscosity was reported 16 times (12.2%). Transient difficulty in swallowing was reported by 4 patients (3.1%), presumably mostly as a result of altered saliva consistency, although diffusion of toxin into surrounding tissue cannot be excluded as a cause. Eight children showed temporarily deteriorated feeding behavior (6.1%), while 9 patients showed improved feeding (6.9%). Two patients reported xerostomia after 8 weeks (1.7%), which had resolved after 32 weeks.

Secondary beneficial effects following injection included improved oral hygiene (reduced perioral dermatitis or reduction in halitosis) in 4 patients (3.1%) and improved speech in another 4 patients. These effects generally disappeared after 32 weeks.

DISCUSSION

To our knowledge, this is the largest described series of patients treated for drooling with intraglandular botulinum toxin. In these 131 patients, we found an objective and subjective response rate of approximately 50%, similar to that found in smaller studies. Responders benefited from injection for a median of 22 weeks. After 33 weeks, 25% of initial responders (11.3% of the entire population) still showed a clinically significant response to the toxin, with a handful of patients experiencing continued drooling relief after 1 year.

Morbidity associated with the procedure was limited. Changes in the viscosity of saliva were reported very frequently but rarely led to severe problems, perhaps partially as a result of the dietary advice given to caretakers to provide only food that was easily mashed or melted for several days following injection. Only 2 patients reported xerostomia, indicating that saliva production from the sublingual, parotid, and minor salivary glands was usually sufficient to maintain a physiologically moist oral cavity.

No predictors for successful treatment were found in this series, although it should be noted that this was not a primary objective of the present study. Motor function was expected to correlate with outcome, but this was not confirmed by these data. A larger sample might be required to detect this; alternatively, other factors might influence response to therapy, such as posture, oral motor function, or diet, data for which were not available for this study. It thus remains unclear why some patients benefit so much more or so much longer from botulinum toxin injection than others. As many patients are currently treated without experiencing meaningful

benefits, more information on factors influencing outcome and duration of effect would be very useful.

It should be noted that injections in our study were limited to the submandibular glands, as these are responsible for 70% of resting saliva production. The parotids mainly secrete during mastication. However, combined injections to the submandibular and parotid glands appear to be used more frequently.[17-19] Our clinical experience hints that combined injections could indeed be slightly more effective than isolated submandibular injections, but there is currently little scientifically sound evidence to support or disprove this impression.

Another important issue surrounding the application of botulinum toxin is still the effect of repeated injections. Prolonged denervation of salivary glands induces atrophy of the gland,[20] and it has been hypothesized that chemical denervation via repeated botulinum toxin injection could bring about a similar effect and thus lead to a permanent reduction in drooling. On the other hand, a recent report has described secondary nonresponse to botulinum toxin type B following repeated injection, implying that there may be a limit to the number of effective treatments with botulinum toxin for some patients.[21] Systematic studies in this area, however, have yet to appear.

Until evidence for a cumulative effect appears, botulinum toxin should be considered a temporary solution to relieve drooling, as the current study underscores. In our tertiary center, submandibular botulinum toxin is used as a first-line treatment for patients for whom oral motor training or behavioral therapy have failed or are not considered feasible. Renewed injections are considered on a case-by-case basis. Combined parotid and submandibular injections are generally reserved for patients with a severely inadequate swallowing mechanism and suspected aspiration or for patients who have not sufficiently responded to submandibular injections. We prefer not to give combined injections to children who are fed orally because the diminished food bolus lubrication might pose a risk in children for whom ample saliva is just barely enough. Reducing salivary flow too much in such cases could potentially impair oral feeding. Surgery is advised if (1) the patient has reached an age when it is unlikely that further development will cure the drooling (usually from approximately 12 years), (2) drooling persists despite repeated botulinum toxin injection, or (3) patients express a desire for a permanently effective solution. We believe that systemic anticholinergic therapy should be prescribed with great caution because (1) it carries the risk of serious adverse effects and (2) the less risky localized anticholinergic therapy via botulinum toxin can be quite effective.

Although the observational nature of our study makes it difficult to make definitive statements about the magnitude of botulinum toxin's effect, our results provide further support for the clinical efficacy of botulinum toxin for drooling in patients with non-progressive neurological disease. Furthermore, they indicate that most patients who initially respond well to injection can expect an effect to last between 19 and 33 weeks. Although the 46.6% success rate might appear low, its safety and efficacy make botulinum toxin a useful first-line invasive treatment if conservative measures have failed. Improved patient selection could perhaps increase the response rate. This, together with the effectiveness of repeated injection and combined parotid/submandibular injection should therefore be areas of specific attention in future studies.

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Chapter 4

Does Motor Performance Matter in Botulinum Toxin Efficacy for Drooling?

SUMMARY

The aim of this study was to define factors that influence therapy outcome of submandibular botulinum toxin injections for drooling in children with cerebral palsy or mental disability. We hypothesized that differences in response may be explained by the variation of dysfunctions in the various cerebral palsy subtypes. We investigated treatment response in 80 spastic and 48 dyskinetic children. Additionally, 28 fully ambulant children with only mental disability were examined. The primary outcomes were the drooling quotient, as well as parotid and submandibular flow rates (measured via cotton rolls placed at the duct openings). Both the DQ and submandibular flow rates decreased following treatment. Ninety-three children showed a reduction of more than 50% in DQ, or more than 30% in submandibular flow. Notably, children who showed a clinically relevant response to injection, also showed a reduction in parotid flow (even though this was not injected). In all three subgroups, non-responders showed an increase in parotid flow. We hypothesize that treatment failure is a result of increased parotid flow, potentially due to inadequate inhibition of the reflex arc of salivary secretion. We were unable to identify factors which can predict which children respond to botulinum toxin before treatment.

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INTRODUCTION

Drooling is normal in the growing child up to the age of 18 months, and is considered abnormal in children over 4 years. This is often the case in children with poor neuromuscular coordination, mental disabilities, or in children who lack structural integrity in their jaws, lips, or oral cavity.[1] It is widely accepted that drooling in cerebral palsy is caused by oral motor dysfunction.[2-5] Children with dyskinetic disorders may be the exception to this rule; in these children abnormal oral movements potentially stimulate the parotid glands and lead to the production of more saliva.[2] Moreover, wheelchair-bound children and those with any degree of intellectual impairment are more at risk of oromotor disorders and excessive drooling. Inadequate swallowing of saliva may increase the risk of aspiration, and the constant presence of saliva can impair communication.[6]

Several prospective, controlled clinical trials, have shown that botulinum toxin type A injection leads to a significant reduction of saliva, with a maximum response 2 to 8 weeks after injection.[7] Botulinum toxin inhibits acetylcholine release at the autonomic terminals of the salivary glands, decreasing their secretion. However, in our 10 years of experience, we have found that up to 30% of children show no clinical response to botulinum toxin type A at all.

We have previously suggested that the aforementioned hyperkinetic oral movements in children with dyskinetic cerebral palsy may lead to constant stimulation of the parotid glands and thus to increased saliva.[2] Another explanation might be that peripheral sympathetic inhibition of salivary reflex secretion is abnormal in non-physiologic conditions, such as after injection of botulinum toxin.[8]

To investigate both possibilities, we performed a cohort study. First, the effect of submandibular botulinum toxin type A on parotid salivary flow in 3 different clinical groups: children with spastic cerebral palsy, children with dyskinetic cerebral palsy, and children with mental disability without cerebral palsy. We hypothesized that treatment efficacy would be similar in all 3 groups, with similar response rates.

Second, the influence of botulinum toxin on saliva viscosity was investigated. Botulinum toxin's anticholinergic properties should lead to a reduction of the watery component of saliva and thus to increased salivary viscoelasticity.[9] Interestingly, the opposite has been reported.[9] The thinning of saliva after botulinum toxin injection may indicate increased reflex salivary secretion from other salivary glands such as the parotids (which tend produce a more watery secretion). Therefore, we

hypothesized that non-responsiveness to submandibular botulinum type A is caused by compensatory parotid flow.

METHODS

Participants

We analyzed data from 126 individuals (aged 3-21 years; mean age 10 years and 11 months; SD 4 years and 11 months; 81 boys and 45 girls) who were screened at the outpatient drooling clinic of the Radboud University Nijmegen Medical Center, The Netherlands, and had subsequently undergone treatment with injection of botulinum toxin type A into the submandibular glands between February 2000 and October 2008. Children were categorized as having cerebral palsy or mental disability on the basis of developmental age and the severity of motor disturbances as assessed by the Gross Motor Function Classification System.[10-12] The children with cerebral palsy were subdivided by predominant motor type.[13] All children demonstrated moderate to severe dysfunctional oral motor control and had a score of 3 or higher on the Teacher Drooling Scale (a 5-point scale to express the clinical severity and frequency of drooling; 5 = constantly wet and leaking saliva, 1 = no drooling).[14] None had undergone previous treatment with botulinum toxin type A or surgery for saliva control.

All medications used to treat drooling or to influence salivary secretion (especially benzodiazepines and neuroleptic drugs) were discontinued at least 3 months before the start of the treatment. No limits were set concerning the use of anti-epileptic drugs and the child's level of cognitive development. Data from children diagnosed with ataxic cerebral palsy subtype, Worster-Drought syndrome, or a progressive neurologic condition were excluded.

Intervention and measurements

an ultrasound-guided injection of botulinum toxin type A was injected bilaterally into the submandibular salivary glands divided over 2 sites per gland with a 25-gauge needle. A total dose of 50 U of Botox (Allergan, Nieuwegein, The Netherlands), diluted with 1.5 mL saline, was used.

Children were evaluated at baseline and 8 weeks after treatment. Two well-trained speech and language therapists conducted all the assessments, which always took place in the morning, 1 hour after the last meal. At each assessment, the medical history was taken, especially regarding feeding, speech, coughing, and salivary aspects.[15] In addition, the parents were asked to register all possible side effects in a diary.

The main outcomes were the drooling quotient (DQ) and salivary flow rates. The DQ is a semiquantitative observational method (expressed as a percentage) representing the actual clinical appearance of saliva loss. It was scored according to the original design: drooling was evaluated during a 10-minute episode. A drooling episode was defined as new saliva present on the lip margin or dropping from the chin, which assessed every 15 seconds (40 observations in 10 minutes).[16]

The swab method was used to measure salivary flow rate. After the oral cavity had been dried with sterile gauze, 3 absorbent dental cotton rolls (Salivette; Sarstedt, Etten-Leur, The Netherlands) were placed in the mouth for periods of 5 minutes: 1 roll under the tongue directly in front of the orifices of the submandibular and sublingual glands, and 2 rolls in the upper vestibules at the openings of the parotid ducts.[17] The cotton rolls were weighed before and after the procedure with an electronic scale, sensitive to 0.01g. The roll under the tongue and the 2 upper vestibules rolls were weighed separately, separating submandibular from parotid flow. The increase in weight during the 5-minute period was converted into milliliters of saliva per minute to determine salivary flow rate.

Data analysis

For the statistical analysis, children were divided into three groups: spastic cerebral palsy, dyskinetic cerebral palsy, and mental disability without cerebral palsy. Initially, all three groups were analyzed together. In second instance, the differences within the two cerebral palsy groups were investigated.

All statistical procedures were done using SSPS 17.0 for Windows (SPSS, Chicago, IL). Data analysis included descriptive statistics, the median salivary flow rates, and the median Drooling Quotient. The median salivary flow rates and Drooling Quotient were compared between the 3 categories using nonparametric statistics (Kruskal-Wallis and Mann-Whitney U tests), to account for for non-normal distribution of these measures. Missing data were rare but on occasion were adjusted by the overall mean of the group.

Multivariable analyses of variance (MANOVA) with a repeated measures structure were used to identify differences in mean submandibular and parotid flow and DQ over time, using the measurement moments as variables. If a significant effect was found, post-hoc testing was performed to determine the differences between the groups. Because we wanted to control the type I error rate, the Bonferroni adjustment for multiple comparison was used.

Therapy response was defined as a reduction of 30% in submandibular flow or 50% reduction in DQ. The 30% demand has been used in previous studies, and stems from the estimated measurement error of the swab method,[17] whereas a 50% reduction in DQ is considered a 'clinically relevant' effect.[7]

Participants were categorized as 'responders' or 'non-responders' to submandibular botulinum toxin type A. A MANOVA with a repeated measures structure was used to identify differences in the mean parotid flow between the responding and the non-responding groups. Additionally, for each group (responsive or unresponsive to botulinum toxin type A), the Spearman's correlation coefficient was calculated to define the magnitude of the associations between spastic or dyskinetic cerebral palsy subtype, mental disability, mobility level, and treatment response.

For all statistics, the level of significance for 2-tailed P-values was set at 0.05.

Ethical considerations

The research was conducted in accordance with national and international ethics standards, and the Regional Committee on Research Involving Human Subjects approved the study. Informed consent was obtained from the parents or caregivers of all the study children.

RESULTS

Table 1 lists the patients' clinical characteristics. All children completed treatment. The only significant difference in the baseline demographic variables between the groups was the mobility level, which differed between the children with mental disability and the total cerebral palsy group ($U = 196.00$; $P < 0.001$) and between the children with spastic and dyskinetic cerebral palsy ($U = 1038.00$; $P = 0.02$).

Because of limitations related to the underlying diagnoses of these children, it was not always possible to obtain the flow rates and DQ in a single measurement session. The flow rates were therefore only available for 109 children at baseline, and for 100 children at the 8-week assessment. The DQ was available for 120 children at baseline, and 109 children at 8 weeks. Missing data (14%) occurred at different assessment moments randomly spread over all children. Table 2 shows the median flow rates, and DQ at baseline and 8 weeks after injection. Table 3 shows the comparison of baseline statistics and treatment response in the various subtype categories.

Table 1 Clinical Characteristics

Characteristic	Spastic CP	Dyskinetic CP	Mental Disability without CP
No. of patients	62/126 (49%)	45/126 (36%)	19/126 (15%)
Affected side	Quadriplegic 58, hemiplegic 4	Bilateral affected	Not applicable
Age, mean (S.D.)	11 y 4 mo (4 y 5 mo)	10 y 2 mo (5 y)	11 y (6 y 4 mo)
Sex (M/F)	43/19	27/18	11/8
DA			
<4 y	34 (55%)	22 (49%)	15 (79%)
4-6 y, IQ <70	11 (18%)	9 (20%)	0 (0%)
4-6 y, IQ >70	2 (3%)	1 (2%)	0 (0%)
>6 y	15 (24%)	13 (29%)	4 (21%)
GMFCS*			All ambulatory
I	0 (0%)	0 (0%)	
II	6 (10%)	2 (4%)	
III	21 (34%)	6 (13%)	
IV	18 (29%)	19 (42%)	
V	17 (27%)	18 (40%)	

Abbreviations: CP, Cerebral palsy; DA, Developmental age; GMFCS = Gross Motor Functional Classification System

* Significantly different between the 3 groups by Kruskal-Wallis test.

Table 2 Median Drooling Quotient and salivary flow rate differences (range) in time between each group

Drooling Parameter	Spastic CP	Dyskinetic CP	Mental Disability without CP
Sm0, mL/min	0.39 (0.08-0.68)	0.38 (0.06-1.09)	0.36 (0.16-0.48)
Par0, mL/min	0.32 (0.0-1.06)	0.36 (0.04-1.25)	0.24 (0.04-0.94)
DQ0, %	22.5 (0.0-80.0)[a]	32.5 (0.0-97.5)[a]	27.5 (0.0-77.5)
Sm8, mL/min	0.22 (0.02-0.85)	0.26 (0.04-0.48)	0.20 (0.04-0.8)
Par8, mL/min	0.27 (0.0-1.12)	0.27 (0.0-0.61)	0.22 (0.0-0.68)
DQ8, %	16.9 (0.0-65.0)	12.5 (0.0-57.5)	15.0 (0.0-27.5)

Abbreviations: CP, cerebral palsy; Sm0, Par0, DQ0, Median submandibular and parotid flow and Drooling Quotient at baseline; Sm8, Par8, DQ8, Median submandibular and parotid flow and Drooling Quotient at 8-week assessment

[a] Significant difference for median Drooling Quotient at baseline between children with spastic and with dyskinetic CP (P = 0.03, Mann-Whitney U test).

Table 3 Results between diagnostic categories

Subtype group	Baseline Statistics	P	Treatment response Statistics	P
Spastic vs dyskinetic CP subtype vs mental disability without CP				
DQ	H(2) = 4.96	0.08	F(2; 123) = 2.59	0.08
Sm	H(2) = 0.46	0.79	F(2; 123) = 0.44	0.65
Par	H(2) = 0.58	0.75	F(2; 123) = 4.67	0.01*
Spastic vs dyskinetic CP subtype				
DQ	U = 1053.00;	0.03	F(1; 105) = 5.01	0.03
Sm	U = 1343.00	0.74	F(1; 105) = 0.60	0.44
Par	U = 1274.00	0.44	F(1; 105) = 8.97	0.01†

Abbreviations: CP = Cerebral palsy, DQ = Drooling Quotient, Par = Parotid flow, Sm = Submandibular flow

Table 4 Characteristics of children who did or did not respond to botulinum toxin type A

All Patients (n = 126)	Response (n = 93)	No Response (n = 33)
Spastic CP*	44/62 (71%)	18/62 (29%)
Dyskinetic CP	35/45 (78%)	10/45 (22%)
Mental disability without CP	14/19 (74%)	5/19 (26%)
Age, mean (S.D.)	11 y 1 mo (5 y 6 mo)	10 y 4 mo (4 y 8 mo)
Sex (M/F)	61/32	20/13
Developmental Age		
<4 y*	52 (56%)	19 (58%)
4-6 y, IQ <70	18 (19%)	2 (6%)
4-6 y, IQ >70	2 (2%)	1 (3%)
>6 y	21 (23%)	11(33%)
Sm0, mL/min (range)	0.42 (0.06-1.09)	0.34 (0.08-0.60)
Par0, mL/min† (range)	0.38 (0.04-1.25)	0.20 (0.0-1.06)
DQ0, % (range)	28.1 (0.0-97.5)	22.5 (0.0-80.0)
Sm8, mL/min (range)	0.18 (0.02-0.54)	0.28 (0.12-0.85)
Par8, mL/min (range)	0.27 (0.0-0.86)	0.27 (0.04-1.12)
DQ8, % (range)	12.5 (0.0-57.5)	17.5 (2.5-65.0)

Abbreviations: DA = Developmental age, Sm0, Par0, DQ0 = Median submandibular and parotid flow and Drooling Quotient at baseline. Sm8, Par8, DQ8 = Median submandibular and parotid flow and Drooling Quotient at 8-wk assessment point

According to our definition, 93 children responded and 33 children did not respond to botulinum toxin type A (Table 4). At baseline, no statistically significant differences between the median submandibular flow rate (U = 1189.50; P = 0.06) and median DQ (U = 1302.50; P = 0.20) were found. The median parotid flow rate, however, did vary significantly between responders and non-responders (U = 1099.00; P = 0.02). Furthermore, we found that responders showed a reduction in both submandibular flow rate as well as parotid flow rate, whereas non-responders showed increased parotid flow following submandibular injection. The difference in parotid flow between responders and non-responders was statistically significant (F(1;124) = 20.92; P < 0.001), and is shown in figure 1. Clinical variables such as developmental age (rs = −0.03; P = 0.71), mobility level (rs = 0.08; P = 0.38), and cerebral palsy subtype (rs = 0.08; P = 0.43) did not significantly correlate with response percentage.

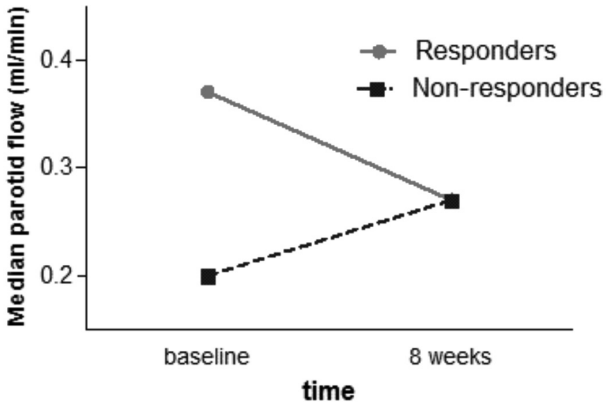

Figure 1 Median parotid flow rate in time between children who did and did not respond to therapy with botulinum toxin type A.

DISCUSSION

This prospective study suggests that submandibular botulinum toxin type A for drooling has similar effects in children with spastic or dyskinetic cerebral palsy, and in those with mental disability without cerebral palsy. We did not find support for the idea that mechanical stimulation of parotid glands dyskinetic cerebral palsy influences treatment outcome. However, our findings did suggest that drooling is clinically distinct between children with spastic and dyskinetic cerebral palsy.

Table 5 Adverse effects after botulinum toxin type A at 8-week assessment

Adverse Effect	Spastic CP (n = 62)		Dyskinetic CP (n = 45)		Mental Disability without CP (n = 19)	
	R	NR	R	NR	R	NR
Increased salivary viscosity	9/62 (15%)	2/62 (3%)	16/45 (36%)	3/45 (6%)	1/19 (5%)	0/19 (0%)
Reduced salivary viscosity	1/62 (2%)	0/62 (0%)	1/45 (2%)	0/45 (0%)	0/19 (0%)	0/19 (0%)
Problems swallowing	2/62 (3%)	2/62 (3%)	2/45 (4%)	0/45 (0%)	0/19 (0%)	2/19 (11%)
Increased frequency of pulmonary infections	3/62 (5%)	2/62 (3%)	1/45 (2%)	0/45 (0%)	0/19 (0%)	0/19 (0%)
Speech problems	1/62 (2%)	1/62 (2%)	0/45 (0%)	0/45 (0%)	0/19 (0%)	0/19 (0%)
Dry mouth	0/62 (0%)	0/62 (0%)	1/45 (2%)	1/45 (2%)	0/19 (0%)	0/19 (0%)
Oral odor	0/62 (0%)	0/62 (0%)	0/45 (0%)	0/45 (0%)	1/19 (5%)	0/19 (0%)

Abbreviations: CP = Cerebral palsy, NR = No response to botulinum toxin type, AR = Response to botulinum toxin type A

Although increased salivary parotid flow rates were found in children who do not respond to submandibular botulinum toxin, the exact role of parotid flow in therapy failure remains unclear. Therapy failure might also be explained by factors that influence the intra-oral management of saliva, such as head position, lip closure, and disturbed oral movements rather than biological factors such as neurologic regulatory mechanisms of salivary flow.

As generally discussed in the cerebral palsy literature, the rate of mental disability and dyskinesia increases as functionality decreases. Based on this, we concluded that our group relatively severely affected.[18,19]

The response rate of 74% was in accordance with the findings of a former study.[7,20] Although our imputation method carries a risk of overestimation of effect, the fact that the missing values appeared to miss completely at random makes this possibility fairly remote.[21]

As mentioned, we found no support for the idea that drooling in children with dyskinetic disorders might be caused by increased production of saliva resulting

from constant stimulation of the parotid glands. However, we feel our data does not entirely rule the hypothesis out. Another explanation could be that the swab method technique itself plays a role: the position of the cottons rolls limits movements of the jaw and tongue, hindering potential salivary gland stimulation in children with dyskinetic cerebral palsy during the assessments. The fact that we did find a relatively higher drooling quotient (where voluntary oral motor function is still possible ("dynamic mouth") in dyskinetic children suggests that mechanical stimulation of the salivary glands might yet contribute to drooling in the dyskinetic subtype. Additionally, children with dyskinetic cerebral palsy seemed to have better residual swallowing functions, as explained by the clear decrease of the drooling quotient after submandibular botulinum application.

Treatment failure was approximately 24% in our study. The reasons for this are not entirely clear. Since ultrasound was used for injection, incorrect application of the botulinum toxin type is unlikely. Adequate doses were used, and response failure due to antibody formation is highly improbable considering the fact that these were first injections. It is also unlikely that chemical diffusion of the toxin via local vasculature or by the influence of gravity caused the parotid flow to decrease because none of the participants experienced bulbar muscle weakness.[22]

One possible explanation for the observed therapy failure might be an inadequate inhibition of the reflex arc of salivary secretion after botulinum toxin application. Saliva secretion is a nerve-mediated reflex, and once the autonomic nerve supply—in particular the parasympathetic nerve supply—has been interrupted, secretion from almost all salivary glands will entirely cease.[23] Under normal conditions inhibition of reflex salivary secretion is centrally controlled. However, under non-physiologic conditions, for instance after botulinum toxin application, peripheral control of salivary secretion comes into action.[24] It might be possible that insufficient peripheral sympathetic inhibition of the salivary secretion played a role in non-responders.

Additionally, the way a child handles saliva might contribute to treatment failure. An earlier study indicated that the response rate can not always be improved by simply injecting the submandibular and parotid glands concurrently. [25] It should be noted that our definition of response was relatively broad, since it was defined as a 30% submandibular flow reduction ("biological factor") or 50% reduction in DQ. If we would have only accepted a 30% reduction in submandibular flow as response, the response rate would have been 65% instead of 76%. Similarly, had we defined 'response' only as a 50% reduction in DQ (linked to the ability to control saliva), the response rate would have been even lower: 47%. This perhaps supports the idea

that the handling of saliva is more important for therapy response than the biological response (ie. the fact that there was a measurable reduction in salivary flow).

We remain unable to predict which patient will respond to botulinum toxin type A. Univariate parameters such as motor impairment ("quality of movement"), mobility level and mental ability ("functional ability"), and even baseline drooling quotient and flow rates had no decisive value in discriminating between therapy response or nonresponse in this study. Remarkably, before injection, an important difference in the parotid flow rates was found between the children who did and did not respond to botulinum toxin type A (figure 1). Unfortunately, we are unable to fully explain this difference.

A potential disadvantage of the present study might be the omission of subjective outcomes.[26,27] However, we wanted to focus on factors that might affect the saliva-control intervention, rather than evaluating the overall effectiveness of the intervention.

In conclusion, it is likely that children with dyskinetic cerebral palsy have better residual swallowing functions and might have higher parotid flow rates. This, however, does not seem to significantly influence the response to submandibular botulinum toxin, as all groups in this study showed similar responses. Future research is needed to provide tools to predict who will respond to therapy and to settle the matter of the contribution of parotid flow in response failure.

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Chapter 5

Failure analysis of submandibular injection of botulinum toxin for drooling: effect of parotid injections

Summary

Aim: To investigate the additional benefit of injection of botulinum toxin into the parotid gland versus the submandibular gland in neurologically impaired children with severe drooling, and to improve overall treatment response.
Method: Neurologically impaired children with intractable drooling were eligible for inclusion (age: 6-24 years). Children were recruited prospectively. Each child underwent submandibular injection with botulinum toxin and was systematically followed-up before, and 8 weeks after injection. Primary outcome parameters were the drooling quotient (DQ) and caretaker VAS. If there was no clinically significant response to injection, children were offered an additional injection of botulinum toxin to the parotid glands, to be administered 16 weeks after the initial submandibular injection. Children were re-evaluated 8 weeks after the parotid injection.
Results: Twenty-one children were enrolled, of which 19 were available for study (11 boys and 8 girls). Both DQ and VAS showed a significant average effect ($P=0.05$ and $P<0.001$). 9 children showed a clinically significant response to submandibular injection (47%). 8 children underwent additional parotid injection. Of these, 4 (50%) subsequently showed a clinically significant treatment response, bringing overall response rate to 68%.
Interpretation: Additional injection of the parotid glands following submandibular injection can improve overall response rate by an additional 50%.

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INTRODUCTION

Drooling is a major clinical problem for 10-58% of children with neurological disease.[1] It is primarily caused by dysfunctional oral motor control, coupled with low oral sensitivity, infrequent swallowing, and poor posture.[2] This can result in anterior (visible) drooling, posterior drooling (aspiration), or both. In anterior drooling, children face problems such as social isolation, hygienic problems, maceration of the facial skin, peri-oral infections or even dehydration.[3-5] Posterior drooling may lead to aspiration pneumonia or potentially asphyxiation.

Over the past decade, botulinum toxin has emerged as a viable treatment for drooling in people with neurological disease. Around the turn of the century, various studies have described its effectiveness in reducing drooling in approximately half of children. The largest report, published by our team in 2010, showed that sub-mandibular botulinum toxin clinically benefits 47% of children for a median of 22 weeks.[6]

To date, there have been no satisfactory explanations for the failure of this treatment to improve the other 53%. One reason that has been frequently mentioned is the possibility that some children may suffer more from activity from the parotid gland than the submandibular gland, which is said to be responsible for 70% of saliva production at rest. We designed an updated treatment protocol to evaluate this hypothesis, in an attempt to improve the response to intraglandular injection of botulinum toxin for drooling.

METHOD

Participants

Children eligible for inclusion were neurologically impaired children with intractable drooling visiting our multidisciplinary drooling clinic for anterior drooling. For each participant, conservative interventions were not expected to lead to an adequate reduction of symptoms. No children had undergone previous invasive treatments for drooling. Full inclusion and exclusion criteria are shown in table 1.

Study design

Children were enrolled consecutively between September 2009 and March 2011. Assessment of the severity of drooling took place under standardized conditions before treatment, and 8 weeks after treatment. This allowed for a within-subjects design where the participant's baseline condition was used as a reference to evaluate the effects of injection over time.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Invalidating drooling (TDS* > 3) or posterior drooling (aspiration of saliva)	Previous salivary gland surgery
Neurological impairment	Previous treatment with botulinum toxin to the submandibular glands
Willingness to participate in follow-up scheme.	Missing baseline measurement, or missing >1 follow-up measurement.
	Known hypersensitivity to botulinum toxin

[a] Teacher drooling scale; a TDS of 3 corresponds with "occasional drooling, intermittent throughout the day" (Camp Bruno 1989)[15]

All children were treated with our hitherto standard scheme of submandibular injection of botulinum toxin. If children did not show a clinically significant response to injection (ie. 'non-responders', defined as a reduction <50% of drooling quotient and <30% of visual analog scores – see Outcome Measures), children were offered an additional injection of botulinum toxin to the parotid glands, to be administered 16 weeks after the initial submandibular injection. The four-month interval was chosen to minimize immunogenicity.[7] Children were re-evaluated 8 weeks after the parotid injection.

Procedures

For the injection of the submandibular glands, children were put under general anesthesia, after which a single dose of botulinum toxin type A (Botox; Allergan, Nieuwegein, Netherlands), reconstituted with 0.9% sodium chloride was injected into the submandibular glands using a 25-G needle and a 1 ml syringe. The 1 ml volume was chosen to allow the dose to be fractionated over at least 3 sites in the gland while minimizing the risk of diffusion into surrounding tissues. We used 25U of botulinum toxin per gland. During injection, the dose was fractionated over at least 3 sites in the gland under ultrasound guidance.

For injection of the parotid glands, a similar procedure was followed: 25U of botulinum toxin was fractionated over at least three sites in both glands, while the child was under general anaesthesia.

Outcome measures

The drooling quotient, a direct-observational semi-quantitative method to assess the severity of drooling, served as the primary outcome.[8] The DQ is defined as the percentage of time a person drools and was measured during two sessions (one

while concentrated, one while distracted). Participants were evaluated at least one hour after a meal while awake and sitting erect. Success of therapy was defined as a 50% reduction in DQ from baseline value.

A caretaker visual analog scale (VAS) score reflecting the subjective severity of drooling over the previous 2 weeks served as secondary outcome measure. Caretakers marked the extent of drooling on a 10-cm line following specific instruction. The VAS score was obtained by measuring the position of the mark in millimeters from the right end of the scale on a scale from 0 to 100, with 100 corresponding to severe drooling.

"Treatment response" was defined as a reduction of 50% or more in DQ and a reduction of 30% or more in VAS, for a combined objective and subjective assessment.

Ethical permission

The research was conducted in accordance with national and international ethics standards. As this was an observational study, specific ethical permission was not required. Assessment procedure, interventions and evaluations were according to regular treatment protocol. Caretakers or parents provided informed consent before each intervention.

Statistical analysis

Statistical analyses were performed using SPSS 16.0.1 for Mac OS X (SPSS Inc, Chicago, Ill.). For analysis of the drooling quotient and VAS, we employed descriptive statistics; conducted paired t-tests to assess differences of paired observations; and performed a multivariate analysis of variance (MANOVA) with a repeated measures design to evaluate the treatment response pattern over time, using a within-subjects setup with the measurement moments as within-subject variables. Mauchly's test was performed to investigate sphericity in the group; violations of sphericity were adjusted using the Greenhouse-Geisser correction.

In every case a P-value ≤ 0.05 was considered statistically significant.

RESULTS

Twenty-one children were enrolled in the study. Two were subsequently excluded for failing to show up at the initial 8-week follow-up. This left 19 children available for study, 11 boys and 8 girls. The mean age was 9 yrs 3mo (SD 5y 1mo; range 4-23 yrs); all but one participant was below 17 yrs of age at the time of initial injection. Eighteen children were diagnosed with cerebral palsy, in one case with clinical progression due to intractable epilepsy. One non-ambulant child was diagnosed with psychomotor retardation and bilateral spasticity due to a mitochondrial dysfunction. Ten children suffered from epilepsy. Full participant characteristics are shown in table 1.

Effect of submandibular injection

All children underwent injection of botulinum toxin into the submandibular glands. Analyzing the overall effect of submandibular injection for all children through repeated measures analysis showed a significant reduction in DQ after 8 weeks. From a baseline value of 25.5, the mean DQ fell to 16.1 (Hotelling's trace F=4526; p=0.047). The VAS showed a similar significant result, and fell from 80 at baseline to 51 after 8 weeks (Hotelling's trace F=30607; p<0.001).

After 8 weeks, 9 children had a clinically significant response to submandibular injection (47%) according to our definition (≥50% reduction in DQ, combined with ≥30% reduction in VAS).

For further analysis, the study group was divided in a 'responder group' (n=9) and a 'non-responder group' (n=10). As is to be expected, a significant difference between baseline and 8-week DQ was found in the responder group (32.0 vs. 9.3; P=0.02); in the non-responder group, no such difference was found (19.6 vs. 22.1; P=0.48).

Figure 1 shows the results of submandibular injection on the DQ and VAS in the overall group, and in the responder and non-responder group separately. There is a notable difference in baseline DQ between the two groups, although this was not significant (19.6 vs. 32.8; P=0.19). No baseline difference was found for the VAS.

Effect of parotid injection

All non-responders were offered additional parotid injection. Two declined; one expressed a desire to 'wait and see', and the other said the subjective improvement was 'satisfactory'. Eight children thus underwent additional parotid injection.

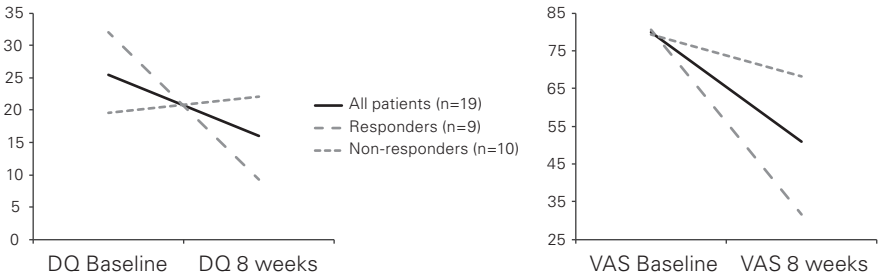

Figure 1 Response to submandibular injection (DQ and VAS). The solid lines show the response of the overall group; the dotted lines of the responders and non-responders separately.

Analyzing the parotid group from initial inclusion to 8 weeks after parotid injection showed a significant response to parotid injection (Hotelling's trace F=6326; P=0.033). From an inclusion value of 18.9, the DQ initially remained virtually unchanged after submandibular injection (19.6), and then fell to 8.0 after parotid injection (p=0.007 compared to baseline). A similar, but non-significant pattern was found for the VAS (Hotelling's trace F=3420; P=0.1). From a baseline value of 78, the VAS showed a non-significant mean reduction to 68 (P=0.084) after submandibular injection, and 45 after parotid injection (P=0.033, compared to baseline).

Figure 2 shows the response to parotid injection, compared to the 'submandibular responder' group. This shows that the 'failures' to submandibular injection, achieve mean outcomes similar to the 'submandibular responders' after parotid injection.

By our definition, 4 children (50%) showed a clinically significant response to parotid injection. This means that, after both injections, the overall response rate for the study group was 68%.

There were no major complications following either injection in the group studied.

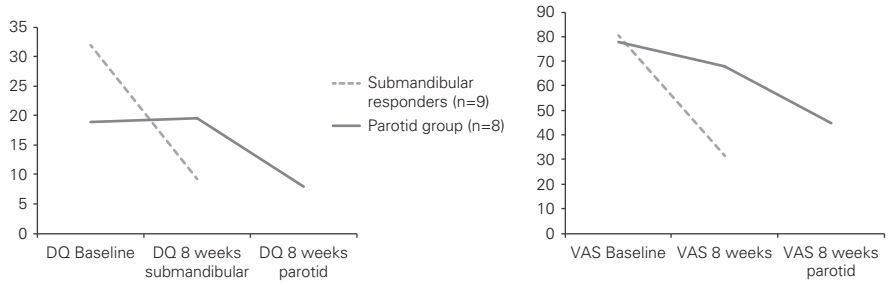

Figure 2 Response to both submandibular and parotid injection in the parotid group, compared with the 'submandibular responders'. Following parotid injection, these children achieve DQ and VAS scores similar to the children who responded to the initial submandibular injection.

DISCUSSION

Although botulinum toxin has been widely adopted for drooling since the turn of the century, there is surprisingly little data on which glands should be treated. Even the recent consensus statement on botulinum toxin for drooling did not find data to make a recommendation on whether to inject the parotid glands, submandibular glands, or both.[9] Each regimen has been tried and reported in international literature.[6,10,11]

Bothwell et al. exclusively injected the parotid glands in 9 children and found that 55% showed a good or moderate response.[12] Similarly, Savarese et al. found that 53% of a group of 21 children showed 'marked improvement' following parotid injection.[13] Our own experience with 131 children demonstrated a response of 47% 8 weeks after submandibular injection.

Most clinics appear to have standardized on injection of both the parotid glands and submandibular glands simultaneously. A randomized study by Reid et al. in 25 children showed a satisfactory response in approximately 68% of children injected in both the submandibular and parotid glands, and another 16% with a 'mediocre response', based on the subjective Drooling Impact Scale.[11]

The potential downside of simultaneous injection of both parotid and submandibular glands, however, is that the added reduction of (serous) parotid secretions can increase post-injection morbidity, such as a dry mouth and dysfunctional swallowing. In the

aforementioned study by Reid et al., 16% of children experienced thickened saliva, and an unspecified number of participants noticed increased difficulty swallowing food. Although formal comparisons are hard to make, this appears slightly higher than our results with submandibular injection, and our clinical experience suggests that combined injection does lead to slightly more morbidity.

Our centre initially chose to only inject the submandibular glands, responsible for 70% of resting saliva, to minimize such adverse effects. The current study was an attempt to improve the response rate to botulinum toxin injections while acting minimally invasive, and to investigate the relative merits of administration to the parotid and submandibular glands. Our hypothesis was that children who failed to respond to submandibular injection could benefit from an additional parotid injection, especially as it has been shown that submandibular injection can lead to a compensatory increase in parotid flow.[14] The benefit of a two step approach is that the responders did not have their parotid glands needlessly injected.

Following submandibular injection, we found a result that was in line with our earlier published results. Half of the 53% "non-responders" who chose to undergo additional parotid injection, became 'responders' after parotid injection; ie. 68% of enrolled children ultimately showed a clinically relevant response to botulinum toxin in this two-step approach.

There are several potential explanations for the improved response rate following additional parotid injection. One is that the submandibular injections lead to a compensatory parotid flow. A second, less likely, option is that the submandibular gland was not sufficiently denervated following injection and continued to function. A third possibility is that non-responders suffered from combined parotid and submandibular drooling, and submandibular injection reduced the overall extent of saliva production, but not sufficiently to result in a clinically relevant reduction in drooling. A fourth explanation is that non-responders to submandibular injections suffered from mainly parotid gland activity.

None of these can be conclusively ruled out based on available data. A recent study, performed in our centre in 128 children, showed that children who do not respond to submandibular botulinum toxin demonstrate an increase in absolute parotid flow rate. Since we have stopped measuring flow rates, a similar analysis could not be performed for this study.[2] However, we believe that this, coupled with the observations in the present study, suggests that non-responders might constitute a group of clinically different children that suffer more from parotid activity.

If it is indeed the case that there are 'parotid droolers' and 'submandibular droolers', this would be a relevant observation for two reasons. First, it would be the first potential predictor of botulinum toxin outcome. Second, it would have implications for other drooling treatments – both invasive (surgical) and non-invasive treatments should then be targeted at the 'dominant glands' in an individual child. Although it remains to be seen how 'parotid droolers' and 'submandibular droolers' could be clinically distinguished, the possibility that individual gland activity determines treatment outcome deserves to be further investigated in a larger setting.[15] In the case of repeated botulinum toxin injections, successive injections could potentially be limited to the 'dominant glands'.

In conclusion, our study shows that additional injection of the parotid glands following submandibular injection can improve the response rate by an additional 50%. On average, injection of the parotid glands in 'non-responders', leads to a reduction of objective and subjective drooling parameters similar to 'responders' to submandibular injection. We feel this two-step approach offers the benefits of potentially reduced morbidity and cost of treatment, while providing improved short-term drooling relief. Future studies should determine if these results can be reproduced in larger groups.

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Chapter 6

Botulinum toxin vs. submandibular duct relocation for severe drooling

SUMMARY

Aim: Botulinum neurotoxin type A (BoNT-A) has been described as an effective intervention for drooling and is being increasingly adopted. However, its effectiveness compared with established treatments is still unknown. We undertook a within-participants observational study to examine this.

Method: A historic cohort was formed of 19 children and young adults (10 males, nine females) with severe drooling who underwent BoNT-A injections followed by surgical re-routing of the submandibular duct at least 6 months later. Mean age at time of admission was 11 years 5 months (range 5–17y) and mean age at the time of surgery was 14 years (range 6–23y). Fifteen children were diagnosed with bilateral cerebral palsy (CP), three with unilateral CP, and one with non-progressive developmental delay. Gross Motor Function Classification System levels were the following: level I, n=1; level II, n=2; level III, n=7; level IV, n=6; and level V, n=3). The primary outcome was the drooling quotient, which was assessed before each intervention and 8 and 32 weeks thereafter. A multivariate analysis of variance of repeated measures was performed, with the measurement points as the within-participant variables.

Results: The drooling quotient was reduced to a greater extent after surgery than after BoNT-A administration ($p=0.001$). Compared with a baseline value of 28, the mean drooling quotient 8 weeks after surgery was 10, and 32 weeks after surgery was 4 ($p<0.001$). Among the group treated with BoNT-A, the drooling quotient showed a significant reduction from a baseline value of 30 to 18 after 8 weeks ($p=0.02$), and a continued but diminished effect after 32 weeks (drooling quotient 22; $p=0.05$).

Interpretation: Both interventions are effective, but surgery provides a larger and longer-lasting effect.

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INTRODUCTION

Drooling is a significant problem for many people with neurological disorders. In particular, children with cerebral palsy (CP), the most common paediatric physical disability, are frequently affected. Approximately 10 to 37% of children with CP suffer to some degree from drooling,[1] mostly as a result of poor oral sensitivity, spasticity, and infrequent swallowing, coupled with insufficient control of the mechanism for coordinating the activity of the orofacial, palatolingual, and head and neck musculature. This leads to excessive pooling of saliva in the anterior oral cavity and, consequently, to unintentional saliva loss.[2,3] Although the amount of drooling varies depending on the severity of the associated developmental disorder, the lifelong physical and emotional consequences for both children and caregivers have been amply described. These can include stigmatization, impaired self-esteem, and community exclusion, as well as chronic dryness and irritation of the facial skin. Personal hygiene can also be cumbersome, as some children require multiple daily clothing changes as a result of their drooling.

A wide range of treatments have been proposed over the years, including correction of situational factors, speech therapy, biofeedback therapy, various pharmacotherapeutics, radiotherapy, and a range of surgical methods. Surgery to the salivary duct or gland might well be the best-established treatment, especially for severely affected children in whom conservative measures do not provide adequate relief.[4] Of the several surgical procedures described, submandibular duct relocation (SMDR), with or without excision of the sublingual gland currently seems favoured by most professionals. By relocating the papillae of the submandibular ducts from the anterior oral cavity to the base of the tongue, saliva from the submandibular glands is able to flow directly into the oropharynx. Numerous studies have reported SMDR to be effective and well tolerated.[5-9] For obvious reasons, this particular procedure is not suitable for children with a high risk of aspiration (posterior drooling).

In the last decade, injection with botulinum neurotoxin type A (BoNT-A) has emerged as the most serious alternative to surgery for children with severe drooling and has attracted substantial worldwide attention.[10-16] A potent anticholinergic agent, botulinum toxin cleaves to SNAP-25 (an enzyme involved in the release of acetylcholine at the presynaptic membrane of parasympathetic nerves) to cause temporary functional denervation of the target organ. As the secretion of saliva is principally mediated by parasympathetic activity, injection of BoNT-A into two or four major salivary glands results in a clinically appreciable reduction in salivary flow for approximately six months, after which the treatment needs to be repeated.

Despite the evidence supporting the effectiveness of BoNT-A in the treatment of drooling, its relevance remains to be defined. Only two studies have directly compared it with another intervention (scopolamine patches).[10-12] Others have merely compared it with either 'no treatment' or with placebo, or have lacked a comparison altogether.[14-16] Considering the increasing use of botulinum toxin for drooling, the lack of information regarding its effectiveness compared with more established treatments is becoming increasingly in need of redressing.

In this study we compare botulinum toxin with surgical relocation of the submandibular duct by analysing the effect on the drooling quotient in children and young people who have undergone both procedures. Relative reductions of validated methods to quantify the amount of drooling were analysed. The null hypothesis that the effect of surgery and BoNT-A would be equal was tested.

METHODS

Participants

Participants were recruited from the multidisciplinary drooling clinic of the Radboud University Medical Centre in Nijmegen, the Netherlands, between January 2001 and July 2008. The source population consisted of children who were initially treated in our clinic with submandibular botulinum toxin. Children in this group who were subsequently scheduled to undergo SMDR with excision of the sublingual gland were eligible for inclusion in the study (Table I). Surgery was generally performed because of a parent's wish for a permanent solution to persistent drooling problems.

A score of 3 or higher on the Teacher Drooling Scale was required for inclusion. This corresponds to at least occasional drooling, intermittent throughout the day. No limits were set with regard to the children's level of cognitive development. Full inclusion and exclusion criteria are shown in Table 1.

Study design

A historic cohort was formed in which each child was first treated with botulinum toxin to the submandibular glands and subsequently underwent SMDR with excision of the sublingual gland. Each child thus formed his or her own comparison, which increases reliability and statistical power in a population as heterogeneous as children with CP. Participants were systematically and prospectively assessed before each intervention, and 8 and 32 weeks thereafter. A washout period of at least 6 months after BoNT-A injection was observed to avoid a carry-over effect.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age 4–24y	Treatment with botulinum toxin less than 6 months before surgery
Invalidating drooling (TDS >3)	More than two subsequent measurements missing
Indicated for submandibular duct relocation surgery after being treated with botulinum toxin to the submandibular glands at least once	Missing baseline measurement
Pharyngeal phase of swallowing clinically intact	
Diagnosed with cerebral palsy or non-progressive developmental disorder	

Abbreviations: TDS, Teacher Drooling Scale.

Procedures

Each child in the study underwent standardized treatment. For the injection of the botulinum toxin, the children received a general anaesthetic, after which a single dose of BoNT-A (Botox; Allergan, Nieuwegein, the Netherlands) was injected into the submandibular glands under ultrasound guidance using a 25G needle and a 1mL syringe. We used 25U/gland, reconstituted with 1mL of 0.9% sodium chloride. The 1mL volume was chosen to allow the dose to be fractionated over at least three sites in the gland while minimizing the risk of diffusion into surrounding tissues.[17]

Surgery was also performed under general anaesthesia. After the papillae of the submandibular ducts were located, the floor of the mouth was infiltrated with local anaesthetic and adrenaline, and an incision was made to create two mucosal islands containing the papilla. The submandibular duct was freed anterior to the posterior, taking special care to prevent damage to the lingual nerve. The sublingual glands were then resected bilaterally to prevent ranula formation. After submucosal re-routing of the submandibular ducts to the posterior oral cavity, the papillae were sutured at the base of the tongue with a single stitch, from the posterior to the glossopharyngeal plica. Children were given a single dose of corticosteroids during surgery and, if necessary, a second dose on the first postoperative day. We routinely prescribed a 7-day postoperative course of antibiotics (co-amoxiclav) with 5 days of diclofenac for pain management.

Outcomes

The drooling quotient, a validated, direct observational, semiquantitative method to assess the severity of drooling, served as the primary outcome measure.[18] The drooling quotient is defined as the percentage of time a person drools and was measured by one of two specially trained speech and language therapists. During two 10-minute sessions (one while the participants were concentrating and one while they were distracted) the absence or presence of new saliva on lip or chin was recorded every 15 seconds, for a total of 40 observations per session. Participants were evaluated at least 1 hour after a meal while awake and sitting erect. For either intervention, success of therapy was defined as a 50% reduction in drooling quotient from baseline value.

Table 2 Demographics

	Boys	Girls	Total
Age at intervention (mean, SD)			
BoNT-A	11.7 (4.2)	11.1 (4.0)	11.4 (4.0)
SMDR	15.3 (4.5)	13.1 (4.6)	14.3 (4.5)
Diagnosis			
Bilateral spasticity	8	1	9
Unilateral spasticity	2	7	9
Non-progressive developmental delay	0	1	1
GMFCS[a]			
I	1	0	1
II	1	1	2
III	3	4	7
IV	4	2	6
V	1	2	3
Epilepsy			
Controlled	4	1	5
Intractable	2	3	5
Developmental age			
<4yrs	4	5	9
4-6yrs, IQ>70	1	0	1
4-6yrs, IQ<70	1	2	3
>6 yrs	4	2	6

[a]**Gross Motor Function (GMFCS).** 1=reduced speed, balance, and coordination, 2=limitations walking on uneven surfaces and inclines, and in crowds or confined spaces, 3=walking indoors or outdoors on a level surface with assistance, wheelchair as needed. 4=reliance on wheelchair. 5=no means of independent mobility

The research was conducted in accordance with national and international ethical standards. As this was an observational study, specific ethics permission was not required. Informed consent was provided by caregivers or parents before each intervention.

Statistical analysis

Statistical analyses were performed using SPSS 16.0.1 for Windows (SPSS Inc, Chicago, IL, USA). For analysis of the drooling quotient, we employed descriptive statistics, conducted paired t-tests to assess differences in paired observations, and performed a multivariate analysis of variance (MANOVA) with a repeated-measures design to evaluate the treatment response pattern over time, using a within-participants set-up with the measurement points as within-subject variables. Mauchly's test was performed to investigate sphericity in the group; violations of sphericity were adjusted using the Greenhouse–Geisser correction. To allow the repeated-measures analysis, missing data were adjusted in the following two ways: by carrying the last observation forward and through a worst case scenario. In the 'carry last observation forward' procedure, missing data were replaced with the last previous observation.[19] As imputation by this way could introduce bias, we also analysed the data in a worst case scenario, whereby missing data were replaced with the baseline measurements. The outcomes of both approaches are presented.

For this study, we selected only children who were to undergo SMDR after being treated with botulinum toxin. To address a potential selection bias against botulinum toxin (i.e. the possibility that only poor responders to botulinum toxin were included), analyses were performed to compare the included group with the entire population of children treated with botulinum toxin in our centre. Unpaired t-tests were used to compare treatment response and age; $\chi 2$ tests were used to compare motor function scores. For all analyses, a p value of ≤ 0.05 was considered statistically significant.

RESULTS

From a source population of 133 children treated with botulinum toxin, 20 children were included in the study. One was excluded because of a complete lack of follow-up data, leaving 19 children (10 males, nine females) eligible for study and analysis (Table 2). Children were a mean age of 11 years when botulinum toxin was administered (SD 4y, range 5–17y) and a mean age of 14 years at the time of surgery (SD 4y 6mo, range 6–23y). Both interventions were generally well

tolerated. One child reported transient difficulty in swallowing after BoNT-A injection. Another child was admitted to an intensive care unit after surgery for postoperative pneumonia and atelectasis.

The drooling quotient was initially analyzed using the data corrected by carrying the last observation forward (see 'Statistical analysis'). Performing a MANOVA of repeated measures with the drooling quotient as the within-participants variable showed a highly significant pattern over time (Hotelling's trace: F=11486; df 5, 14; p<0.001), with surgery resulting in notably greater reductions in drooling than botulinum toxin (Fig. 1). BoNT-A administration resulted in a significant reduction in the amount of drooling after 8 weeks, on average reducing to 18.0 from a mean baseline value of 29.8 (p=0.02). Although the effect appeared to wane after 32 weeks, there was still a significant reduction compared with baseline (mean difference from baseline –7.4; p=0.05). From a baseline value of 27.5, surgery led to a reduction in the drooling quotient to 9.6 after 8 weeks and to 4.1 after 32 weeks (p<0.001). The observed mean difference in baseline measurements between botulinum toxin and surgery was not significant (–2.2; p=0.63), making it unlikely that an actual difference in pretreatment conditions existed.

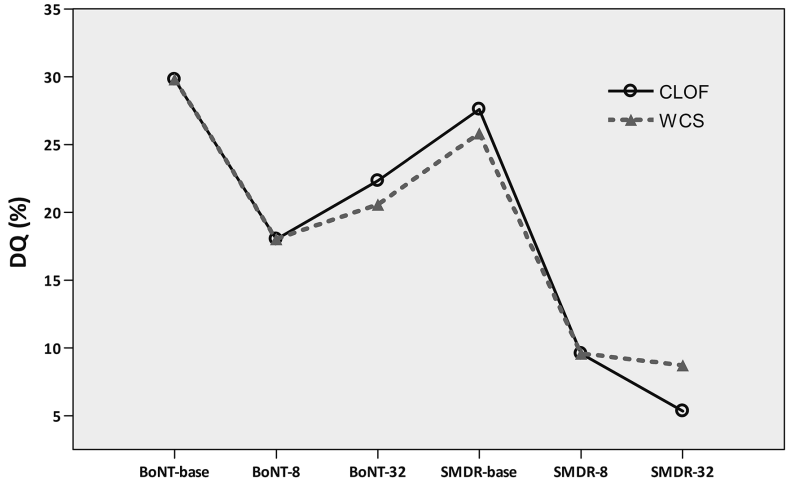

Figure 1 Drooling quotient (DQ): mean in time. LOCF, last observation carried forward; WCS, worst case scenario; BoNT-A, botulinum neurotoxin type A with subsequent follow-ups; SMDR, submandibular duct relocation.

As there were only 10 missing values (out of 114, five at SMDR-32, three at BoNT-32, and one each at SMDR-base and SMDR-8), analysis of the worst case scenario did not provide substantially different results. The pattern was, again, highly significant (Hotelling's trace: F=10818; p<0.001), with surgery performing markedly better than botulinum toxin. Again, no significant difference in baseline values between BoNT-A and surgery was found (mean difference −3.4; p=0.26). The complete effects of both analyses are shown in Table 3.

Table 3 Mean Differences Between Baseline and Follow-up Measurements

			Last observation carried forward		Worst-case scenario	
	Observations	Missing data	DQ[a] (95%-CI)	Sign[b]	DQ (95%-CI)	Sign[b]
Botulinum toxin						
baseline-8 weeks	19	0	11.8 (2.6–21.0)	0.02	11.8 (2.6–21.0)	0.02
baseline-32 weeks	16	3	7.5 (0.1–14.8)	0.05	8.7 (2.6–14.8)	0.01
SMDR						
baseline-8 weeks	17	2	18.0 (10.5–25.6)	<0.001	16.8 (9.5–24.1)	<0.001
baseline-32 weeks	14	5	23.4 (14.2–32.6)	<0.001	20.8 (11.0–30.6)	<0.001

[a] Drooling quotient. [b] With paired-samples *t*-tests, 1-sided P ≤ .05

Defining successful therapy as a 50% reduction in the drooling quotient, seven children could be considered as responders to BoNT-A after 8 weeks and 6 after 32 weeks. After surgery, 15 children showed a significant response after 8 weeks and 16 children after 32 weeks.

To address potential selection bias, the response to botulinum toxin in these 19 children was compared with the entire population of children treated with submandibular botulinum toxin in our hospital (n=133). The reductions in drooling quotient did not differ significantly after 8 (p=0.21) or 32 weeks (p=0.53), indicating that the response to botulinum toxin in the study group was representative of the mean. Age (p=0.38) and global motor function (p=0.86) also did not differ significantly between the children selected for this study and the other children treated with botulinum toxin.

DISCUSSION

To our knowledge, this is the first study to compare botulinum toxin with surgery for drooling. Earlier evaluations of BoNT-A have been limited to comparisons with anticholinergic drugs, placebo, or no treatment, or have lacked a comparison group altogether.[14-16] Our analysis shows significant benefits from both surgery and BoNT-A, but with surgery producing a larger effect in more children.

We found surgery to be effective in 81% of participants. This is in line with other studies; SMDR has a long history, and others have reported success rates of 76 to 90%.6-8 Compared with the 33 to 53% response mentioned in other studies, the 37% we found for botulinum toxin was on the low side of the spectrum, although not extraordinarily so. Both interventions were generally well tolerated, with notable adverse events limited to a single case for each treatment. No child suffered permanent harm after either intervention. Other authors have described similar complication rates.

It could be argued that the formation of an historic cohort introduces a possibility for selection bias. This would be especially evident here because only children who underwent surgery after initial BoNT-A treatment were selected. Our analysis, however, indicates that the study group formed a representative selection of children treated with botulinum toxin at our facility. It has been our experience that most parents or children who choose surgical treatment express a desire for a permanent solution to drooling. This, rather than a disproportionately poor response to botulinum toxin, appears to be the deciding factor in the choice of surgery after initial botulinum toxin injections.

It is worth noting that BoNT-A injections in our study were limited to the submandibular glands to allow the parotid glands to function unimpaired. The submandibular glands are responsible for 60 to 70% of unstimulated saliva production, and the parotids mainly secrete saliva during mastication, which implies that a combined injection would be useful only for children who experience saliva loss mainly when eating. Several other authors have chosen to inject both the parotid and submandibular glands, but there is relatively little evidence that this is more effective than submandibular injections alone.[20]

Our results perhaps allow a cautious estimation of where botulinum toxin fits in the spectrum of management strategies for drooling. On the ‘less invasive’ side of the spectrum, botulinum toxin competes with alternatives such as behavioural therapy and systemic anticholinergic drugs. Systemic anticholinergic drugs appear to be

similarly effective to botulinum toxin, but might be associated with a higher number of side effects.[12] Behavioural and speech therapy are the least invasive, but suitable only for children whose cognitive abilities are sufficient for them to undergo training.[21,22]

On the other side of the spectrum, surgery is more invasive, but probably has a greater effect in more children. Moreover, the results of surgery usually last many years,[6] whereas the temporary nature of botulinum toxin means that timely additional injections are generally required for continued drooling relief. It has been hypothesized that repeated injections would ultimately lead to glandular atrophy and thus potentially a longer-term effect. To date, such an effect has not been described in the literature, and we are not aware of a systematic study into the effects of repeated injections.

Yet there are situations in which botulinum toxin could offer distinct advantages over surgery. Young children could be an example; although the limit for physiological drooling is commonly accepted to be 4 years of age, it is not clear if this also applies to children with developmental disorders. Performing surgery at a very early age could, therefore, be premature, as there may be a possibility that saliva control will spontaneously improve. Botulinum toxin, possibly combined with behavioural therapy, could, in such cases, provide effective drooling relief with minimal morbidity while the child develops. Surgery could then follow at a later stage to provide a more definitive solution if required.

Additionally, there is the interesting possibility of using botulinum toxin as a diagnostic tool. As botulinum toxin's effect is strongly localized, injection into specific glands could assist in determining which gland(s) contributes most to drooling in a particular child. This could facilitate subsequent management decisions. SMDR would, for instance, not be particularly useful if someone is found to suffer mostly from parotid activity. A potential correlation between the outcome of BoNT-A and other therapies would thus allow clinicians to predict the usefulness of other strategies in specific children. Our sample was too small to allow such an analysis, but this deserves attention in subsequent studies.

In conclusion, our study indicates that, although both botulinum toxin and SMDR are safe and effective, the surgical approach offers a significantly larger effect and is beneficial for more children. Botulinum toxin offers some unique characteristics, but it should be noted that there are still some uncertainties concerning its application, for example the relative effects of combined parotid and submandibular injections and submandibular-only injections, the effect and cost-effectiveness of

repeated injections, and the efficacy compared with traditional first-line treatments such as behavioural therapy and speech therapy. Although there can be little doubt that botulinum toxin is a valuable addition to the management of drooling, the extent to which it is currently used might not fully reflect the uncertainties still surrounding its application. This may partially find its origin in the enthusiasm accompanying a radically new treatment approach, but deserves critical reflection and additional study.

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Chapter 7

Salivary duct ligation for anterior and posterior drooling

SUMMARY

Objectives: To analyze the effectiveness and morbidity salivary duct ligation to treat anterior drooling and posterior drooling (aspiration) in a standardized, prospective setting, for children with neurological disorders.
Design: Prospective cohort study. Patients were included consecutively and prospectively evaluated using a standardized follow-up schedule: before surgery, 8 weeks after surgery, and 32 weeks after surgery.
Participants: Children diagnosed with cerebral palsy or another neurological disorder suffering from moderate to severe anterior or posterior drooling
Main Outcome Measures: Direct-observational drooling quotient (DQ), caretaker Visual Analog Scale scores (VAS), and incidence of pneumonias.
Results: 21 patients were included. Fifteen children underwent 2-duct ligation, 3 underwent 3-duct ligation, and 4 4-duct ligation. Duct ligation led to significant objective and subjective improvement in anterior drooling. The DQ fell from a baseline value of 27 to 8 after 8 weeks(P=0.001) and 12 after 32 weeks (P=0.06). The VAS fell from 85 to 48 (P=0.001) after 8 weeks and to 52 after 32 weeks (P=0.003). Although duct ligation appeared to reduce the number of aspiration pneumonias in posterior drooling, no statistical significance was reached (P=0.23).
Conclusions: Salivary duct ligation shows promise for the treatment of both anterior and posterior drooling. It is a relatively simple procedure that shows significant short term effect on anterior drooling, and potentially reduces aspiration pneumonias in posterior drooling.

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INTRODUCTION

Drooling is a major clinical problem for 10-58% of children with neurological disease.[1] It is primarily caused by dysfunctional oral motor control, coupled with low oral sensitivity, infrequent swallowing, and poor posture. This can result in anterior (visible) drooling, posterior drooling (aspiration), or both.

The morbidity associated with drooling has been widely described, and as a result various surgical and non-surgical treatments are employed. It seems generally agreed that surgery is the most effective permanent solution, but should be considered a last resort due to its invasiveness,.

Recently, ligation of submandibular or parotid ducts has been promoted as a less invasive alternative to other surgical procedures. Various reports have described experiences with this procedure, but the results have sometimes been conflicting and the number of patients limited.[2-5] In the present study, we present the effectiveness and morbidity of this procedure to treat anterior and posterior drooling (aspiration) in a standardized, prospective setting.

METHODS

Ethical considerations

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

Participants

Children eligible for inclusion visited our university multidisciplinary drooling clinic with intractable drooling due to cerebral palsy or another neurological disorder. For each participant, conservative measures did not, or were not expected to produce an adequate reduction of symptoms, and there was a contra-indication for our standard surgical technique (submandibular duct relocation). Inclusion and exclusion criteria are shown in table 1.

Study design

Patients were enrolled consecutively between July 2006 and July 2010. Assessment of the severity of drooling took place under standardized conditions per our standard follow-up protocol: before treatment, and 8 weeks and 32 weeks after treatment.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Invalidating drooling (defined as a TDS[a] > 3) or aspiration	Previous salivary gland- or duct surgery
Surgical indication due to inadequate effect of conservative measures	Missing baseline measurement, or missing >1 follow-up measurement.
Diagnosed with cerebral palsy or other neurological disorder	
Contra-indication to submandibular duct relocation (eg. inadequate pharyngeal phase of swallowing or aspiration), or express desire for ligation	
Willingness to participate in follow-up scheme.	

[a] Teacher drooling scale; a TDS of 3 corresponds with "occasional drooling, intermittent throughout the day"

Three subgroups were formed: (1) anterior drooling, (2) anterior drooling and limited posterior drooling, and (3) posterior drooling. For anterior drooling groups (1) and (2) were jointly analyzed, and for posterior drooling groups (2) and (3).

Procedures

Children in the study underwent either ligation of both submandibular ducts (2-duct ligation), both submandibular ducts and a single parotid duct (3-duct ligation), or of all submandibular and parotid ducts (4-duct ligation). 4-duct ligation was reserved for children with severe posterior drooling and no significant oral intake. The choice between 2- and 3-duct ligation in an individual patient was a consensus decision mainly based on the extent of oral intake; children with significant oral feeding would generally undergo 2-duct ligation to fully maintain the beneficial effects of parotid saliva for mastication.

Each procedure was performed under general anesthesia, as described elsewhere.[2] Initially, all ducts were ligated using non-resorbable polyester 3.0 sutures. From June 2008, metal vascular clips in a disposable stapler were used.

Outcome measures

Anterior and posterior drooling were analyzed separarately. For anterior drooling, the drooling quotient (DQ), a validated, direct-observational semi-quantitative method to assess drooling, served as the primary outcome.[6] The DQ was measured

by a specially trained, unblinded speech language therapist. Treatment response was defined as a 50% reduction in DQ from baseline.

A caretaker visual analog scale (VAS) score reflecting the severity of drooling over the previous 2 weeks served as secondary outcome measure. It was scored from 0-100, with '100' corresponding to 'severe drooling'.[6]

For posterior drooling, the number of aspiration pneumonias requiring antibiotic treatment was compared in the year before surgery to the 32 weeks after surgery. Data was gathered from hospital charts and a survey of included patients.

Statistical analysis

Analyses were performed using SPSS Statistics 20.0.0 for Mac. For analysis of the DQ and VAS, we employed descriptive statistics; conducted paired t-tests; and performed a multivariate analysis of variance (MANOVA) with a repeated measures design to evaluate the treatment response over time, using a within-subjects setup with the measurement moments as within-subject variables. Missing data were adjusted in two ways: by carrying the last observation forward (LOCF), and by carrying the baseline observation forward (worst-case scenario; WCS). The outcomes of both approaches are presented.

For analysis of pre- and post-operative incidence of aspiration pneumonias, we used descriptive statistics and Wilcoxon's Signed-Rank test.

A P-value ≤ 0.05 was considered statistically significant.

RESULTS

23 patients were enrolled, 14 boys and 9 girls. Two were subsequently excluded due to a complete lack of follow-up data: in one case, severe oral hyper-responsiveness made reliable follow-up measurements impossible, and another was lost to follow-up. 21 children were thus available for analysis. The mean age was 13 yrs. 7mo (SD 3y 11mo; range 7-20 yrs.). Full participant characteristics are shown in table 2.

Fifteen children underwent 2-duct ligation, 3 underwent 3-duct ligation, and 4 4-duct ligation. The median surgical time was 27 minutes for 2-duct ligation, 34 minutes for 3-duct ligation, and 55 minutes for 4-duct ligation. During the study period, 35 children underwent surgical procedures other than duct ligation (such as submandibular duct relocation).

Table 2 Patient characteristics

Neurological condition		
Cerebral palsy		16 (76%)
Other	Progressive	2 (10%)
	Non-progressive	3 (14%)
GMFCS[a]		
Grade I, II or III		3 (14%)
Grade IV		4 (19%)
Grade V		14 (67%)
Epilepsy		
No		5 (24%)
Controlled		6 (29%)
Intractable		10 (48%)
Drooling		
Anterior		4 (19%)
Anterior and posterior		7 (33%)
Posterior		10 (48%)
Gastroesophageal reflux		14 (67%)

[a] Gross Motor Function Classification System[10]

Table 3 Effect on anterior drooling per intervention

	DQ (95%-CI)		VAS (95%-CI)	
	LOCF	**WCS**	**LOCF**	**WCS**
2 months (compared to baseline)				
2DL	-19.0 (-30.1 – -7.1)	-19.0 (-30.1 – -7.1)	-38.2 (-59.0 – -17.4)	-38.2 (-59.0 – - 17.4)
3DL	-17.5 (–145 - 110)	-17.5 (–145 - 110)	-28.5 (-60.2 – 3.3)	-28.5 (-60.2 – 3.3)
Overall	-18.8 (-28.5 – -9.2)	-18.8 (-28.5 – -9.2)	-36.5 (-52.9 – -20.0)	-36.5 (-52.9 – -20.0)
8 months (compared to baseline)				
2DL	-16.0 (-35.8 – 3.8)	-13.8 (-33.9 – 6.4)	-37.3 (-59.6 – -15.1)	-32.7 (-56.8 – -8.6)
3DL	-10.6 (-50 – 29)	-10.6 (-50 – 29)	-13.0 (-25.7 – -0.3)	-13.0 (-25.7 – -0.3)
Overall	-15.1 (-30.6 – 0.4)	-13.3 (-29.0 – 2.5)	-32.9 (-51.5 – -14.3)	-29.1 (-48.7 – -9.5)

LOCF, last observation carried forward; WCS, worst-case scenario.
Based on paired-samples t-tests, 2-sided $P \leq 0.05$.

Anterior drooling

Eleven children suffered from significant anterior drooling. Nine children underwent 2-duct ligation, and 2 underwent 3-duct ligation.

Surgery led to a significant reduction in both DQ and VAS. For the DQ, a highly significant pattern was found (Hoteling's trace F=10808, P=0.004). From a mean baseline score of 27.1, the DQ fell to 8.3 after 8 weeks (P=0.001) and 12.0 after 32 weeks (P=0.06; Figure 1). Similarly, the VAS showed significant improvements in the 32 weeks following surgery (Hoteling's trace F=10971, P=0.004; Figure 1)

Following our definition, 73% of children could be classified as responders after 8 and 32 weeks.

Posterior drooling

Seventeen children had problems related to posterior drooling (6 boys and 11 girls; mean age 13y 10mo). Ten had symptoms limited including recurrent upper or lower respiratory tract infections.

Seven children had multiple aspiration pneumonias in the year prior to surgery (median no. of episodes: 2; range: 1-6; IQR: 1-2.5). Two underwent 4-duct ligation, and four 2-duct ligation. In one case, 3-duct ligation was performed despite severe aspiration, as there was a desire to maintain a limited amount of oral intake.

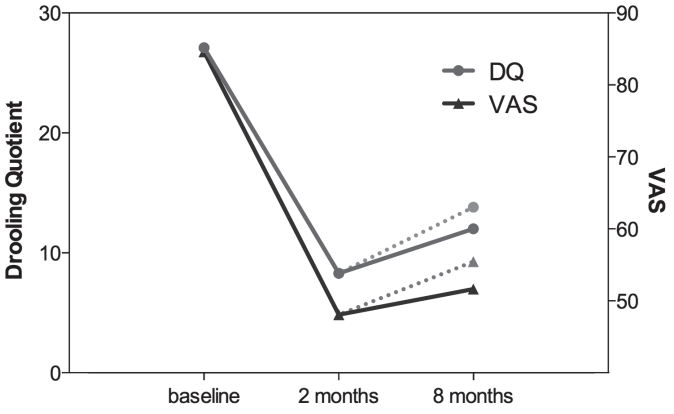

Figure 1 Drooling quotient (red; left Y-axis) and VAS (blue; right Y-axis); mean over time. For both DQ and VAS, the last-observation-carried forward analysis is shown in a solid line, and the worst-case analysis in a dotted line.

Of these seven, 5 did not experience aspiration pneumonias in the 32 weeks following surgery (range: 0-3; IQR: 0-1); there was one treatment failure following 2-duct ligation, and one following 3-duct ligation. The difference in pre- and post-operative incidence of pneumonias was not significant (P=0.23), presumably due to the small sample size.

Four children used prophylactic antibiotics for earlier aspiration pneumonias or recurrent upper airway infection pre-operatively. These were discontinued in three cases, without adverse consequences.

Complications

There were four notable complications. After 4-duct ligation, one child experienced airway obstruction with imminent respiratory insufficiency and was admitted to a pediatric intensive care unit, presumably due to bacterial airway infection. Another child was diagnosed with sialoadenitis with a persistent fistula requiring excision of the sublingual gland. One child required prolonged antibiotic treatment for a floor-of-mouth cyst. Another child developed bilateral ranulas 3 and 4 months after 2-duct ligation; both were excised with the sublingual gland.

Two children underwent bilateral submandibular gland excision because the effect of 3- or 4-duct ligation had not been satisfactory.

DISCUSSION

Synopsis of key findings

This study into the effects of salivary duct ligation is the largest to date to investigate both anterior and posterior drooling in a standardized, prospective setting. It shows that the procedure is effective for anterior drooling on both objective and subjective outcome scales. No significant improvement in aspiration pneumonias was found, although this is possibly a result of the relatively low number of patients with aspiration pneumonias.

Comparison with other studies

A number of studies have addressed the efficacy of salivary duct ligation, with somewhat varying results.[2,4,5,7,8] It should be noted that there is little data on the long-term effect of duct ligation; the study with the longest follow-up described relatively poor overall long-term results, and a reintervention rate of 16%.[5] In our series, two children required renewed surgery in the year following duct ligation owing to inadequate results. However, we have noticed several children required additional surgery after the study, so this number may well rise over time.

The mechanism for such late recurrence is unclear, as duct ligation in animal models has been shown to cause gland atrophy.[9] During re-interventions, we have observed that the ligatures on the ducts often appear intact. It therefore seems likely that an alternative salivary path develops in these patients.

Clinical Implications

The scarcity of long-term data makes it difficult to make firm statements on the value of duct ligation compared to other treatments. Ligation has potential advantages over techniques such as duct rerouting or gland extirpation, which require significantly longer surgical times, more extensive dissection, external scars, and a longer hospital or ICU-admission (if there is a risk of floor-of-mouth swelling). However, these advantages are to some extent offset by the fact that duct ligation does not seem to match 80% reported success rate of the other techniques, and could have a higher re-intervention rate.[10]

Conclusion

Salivary duct ligation is a simple procedure that shows significant short-term effect on anterior drooling, and could potentially reduce posterior drooling. Subsequent studies should focus on long-term follow-up, and efficacy of the procedure compared to other treatments.

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Chapter 8

General Discussion

This study was intended to improve the understanding of the effectiveness of common invasive treatments for severe drooling in children with cerebral palsy, and to assess the relative advantages and disadvantages of each, to aid the formation of an evidence-based management strategy that couples maximum efficacy with minimal morbidity.

The study showed that both botulinum toxin and two surgical methods are effective treatments of drooling, and are relatively well tolerated. Both subjective and objective outcome measurements showed significant improvements following treatment. The duration of the effect varied per intervention, with botulinum toxin generally showing an effect lasting for a median of 22 weeks, and surgery a potentially 'lifelong' effect.

The following paragraphs will provide a brief summary on the main study findings, and reflect on their significance for clinical practice.

BOTULINUM TOXIN FOR DROOLING

Our study provided further evidence for the efficacy of botulinum toxin when measured both by objective and subjective outcomes. Our prospective analysis of 131 children showed a reduction of more than 50% of the drooling quotient in 46.6% of children 8 weeks after treatment. Although in line with earlier studies, this is the largest report of the success of botulinum toxin when routinely employed on a larger scale.

Further analysis showed that responders to botulinum toxin can expect its effect to continue for a median of 22 weeks. A quarter of patients show continued effect after 33 weeks, and a number have even showed a strong response one year after injection. The reason for this inter-individual variability is not known at present, and our study design did not allow this analysis.

Although the 46.6% might be considered low (more than half of patients do not show clinically significant improvement following injection), it should be borne in mind that even those participants who do not qualify as 'responders' might demonstrate some improvement in daily life. Moreover, the fact that intraglandular botulinum toxin has so few serious complications and that its effects are almost by definition temporary make it an almost ideal first treatment in patients where conservative measures have not provided adequate improvement, or are not feasible. When administered properly, there is little harm in trying – its works quickly, and side effects are almost always transient and rarely of serious consequence.

Few treatments for severe drooling can make the same claim. Less invasive (training) techniques can be tedious, and it usually takes months before any effect becomes apparent – if it does at all. Surgery, obviously, is effective but associated with more morbidity and is usually irreversible. Systemic anticholinergics share several of botulinum toxin's benefits: their effects are usually quick, and lowering dosages or stopping medication easily treats adverse events. Evidence levels for application in children with cerebral palsy, however, remain low.[1] Furthermore, unlike botulinum toxin, the systemic availability of these compounds means that there is a greater risk of anticholinergic side effects in organs other than the salivary glands. A recent study in elderly with Parkinson's disease has renewed interest in systemic anticholinergics such as glycopyrolate. There is still relatively little data regarding its effectiveness and safety in children, but considering the fact that side effects generally resolve with the discontinuation of the drug, it is worth trying in certain instances.[2]

Botulinum toxin has the advantage of not requiring daily admission and rarity of systemic side effects. Still, significant questions regarding the application of botulinum toxin have remained. Perhaps the most elusive is the question of the response rate of approximately 50%. Why doesn't the other half show any benefit? Our research suggests that approximately 70% of patients injected with botulinum toxin show reduced salivary flow rates.[3] This indicates that in 30% of children, botulinum toxin does not significantly affect the gland parenchyma, possibly as a result of a sub-optimal dose, or antibody formation against the toxin. It makes clinical sense that these patients do not improve following injection.

However, this still means that approximately 30% of children who show a measurable reduction in flow rate, do not show a clinically notable reduction in drooling. As outlined in chapter 4, CP-subtype and level of intellectual development do not appear to be a factor in this 'response disparity'. A potential explanation might be the influence of the parotid glands, as well as the way specific children handle saliva. This was perhaps illustrated in a recent study in 128 children which demonstrated that the combination of head position, lip seal, voluntary tongue control, developmental age and mobility level were related to treatment outcome when analyzed in a multivariate setting.[4] These factors together were concluded to affect approximately 30% of the response to botulinum toxin.

The results presented in chapter 5 suggest that there is a potential benefit of injecting the parotid glands as well as the submandibular glands. Four of the eight included children responded well to additional parotid injection, even though submandibular injection had failed to yield a response.

The added injection of parotid glands could therefore be considered if submandibular injection does not provide adequate drooling relief, but perhaps should not be performed as a "standard treatment": combined injection has more potential side effects such as xerostomia, or eating problems (due to inadequate lubrication of food boluses).

It is tempting to conclude that drooling is the result of an imbalance between the 'saliva handling capacity' of an individual, and the amount of saliva produced. Unfortunately, pre-intervention patient selection remains very difficult; even though several factors have been identified that can explain treatment failure following botulinum toxin injection, it is still virtually impossible to make predictive statements about which patients will respond to injection. Treatment advice, therefore, remains a best guess.

One aspect of botulinum toxin treatment that was not addressed in the present study, but deserves attention in the future, is the question of multiple successive injections. It has been hypothesized that repeated injection could induce gland atrophy and thus cause a permanent reduction in drooling. However, as yet there is no data to support this supposition, and no study has been performed addressing this specific question. Additionally, it is unclear to what extent antibody formation poses a problem for repeated injection into salivary glands.

Regrettably, this lack of data makes it very difficult to provide a solid treatment recommendation in children where repeated injection is necessary; it remains unclear when to stop botulinum toxin injections, and resort to other treatments.

SURGICAL OPTIONS FOR DROOLING

As mentioned earlier in this thesis, surgery has long been considered to be a benchmark in the treatment of drooling. Submandibular duct relocation, especially, has been performed frequently, perhaps mostly because of the attractive physiological principle underlying the operation. Experience with the procedure is extensive, even though the evidence for the procedure leaves something to be desired (chapter 2).

This study has hopefully contributed to the available evidence, by directly comparing submandibular duct relocation to botulinum toxin. It was found that submandibular duct relocation led to a significantly greater reduction in the drooling quotient than botulinum toxin. Moreover, the response percentage following submandibular duct

relocation was much higher than after botulinum toxin, and the effect lasted well beyond the study duration of 32 weeks (chapter 6).

Although it could be argued that the design of this study is not ideal, it should be noted that the study setup corresponds well to clinical practice: most children are initially treated with botulinum toxin before surgery is considered. The study, therefore, provides an indication of the effect of surgery that can be expected after initial botulinum toxin injection. It is encouraging that the response rate for surgery was so much higher than for botulinum toxin, as it provides non-responders to botulinum toxin with a viable alternative treatment.

Moreover, the improvement in drooling following submandibular duct relocation appears to last a long time. Long-term reports show only a minority of responders relapse over time;[5] in our clinic, of the 35 children operated between 2000 and 2010, only two have undergone additional therapy for continued or renewed drooling (in one child a parotid duct was ligated, and in the other the submandibular glands were excised).

The only significant disadvantages of the procedure are the operative time (approximately 2 hours), peri-operative risks and morbidity. The risk of floor-of-mouth swelling described in various studies means that careful observation is mandatory until approximately 24 hours after surgery; in our clinic children remain intubated on an intensive care unit and only return to a normal ward the day following the operation. Children remain in the hospital until normal eating and drinking is restored, which usually takes 2 to 3 days.

Although many patients and caretakers ultimately feel that the benefits of the procedure outweigh the risks and morbidity, this makes it an unattractive first-line treatment. As a result, surgery is not infrequently postponed until all other avenues have been explored, while children are under-treated in the meantime.

Salivary duct ligation showed great promise to address this dilemma, and our initial results indicate that it is indeed an effective procedure to treat both anterior and posterior drooling (chapter 7). For reasons not entirely clear, the response to duct ligation does appear to be slightly worse than to submandibular duct relocation. The most logical explanation is drainage of saliva via backflow from the obstructed Wharton's duct to the ducts of the sublingual gland, and into the oral cavity, or the formation of new ducts as a response to continued pressure of saliva from the secreting gland. Studies in animal models shows that perfect ligation of salivary gland ducts results in gland atrophy, but it is unclear if this can be accomplished in humans.[6,7]

Nonetheless, our results suggest that salivary duct ligation is more effective than injection of botulinum toxin. And the notably reduced peri-operative morbidity and admission time –most children are treated in a daycare setting–, means that patients or caretakers are frequently more willing to consider the surgical approach. The procedure appears to be considered a 'light' version of drooling surgery, with many patients apparently willing to trade the potentially reduced effectiveness for its markedly reduced peri-operative impact.

More importantly, even though the initial response rate to duct ligation is not as high as for submandibular duct relocation, and submandibular duct relocation is not possible after submandibular duct ligation, the surgical options available to failures of submandibular duct relocation are also available to failures of duct ligation: the possibility of additional duct ligation or salivary gland excision. Both procedures are commonly used to augment the effect of submandibular duct relocation, and can also be tried after failed duct ligation.

As the morbidity of the initial procedure is so much lower for duct ligation, it is very well possible that, on a public health scale, the overall morbidity/efficacy-ratio is better for duct ligation than for SMDR, even considering the higher number of re-interventions in mind. Presently, however, there is insufficient data to prove or disprove this hypothesis.

All in all, it appears highly likely that salivary duct ligation will become a much more popular procedure than it is today, and might well displace submandibular duct relocation as the favored technique. More data on its effectiveness and morbidity compared to other treatments (eg. botulinum toxin) is therefore urgently needed.

A PRACTICAL APPROACH TO CHILDREN WITH SEVERE DROOLING

The current literature does not appear to allow the development of a satisfactory evidence-based guideline for the management of drooling. However, some general principles can be distilled from the literature.

First and foremost, a solid method to evaluate patients should be implemented in any centre wishing to treat these children. Standardized objective and subjective methods to quantify the severity of the problem should be used to screen every new patient, and all children should undergo a full evaluation by a paediatric neurologist and speech language therapist to investigate the cause of drooling, and

to obtain a general idea about the neurological prognosis (progressive disease is a relative contra-indication to procedures such as submandibular duct relocation).

Once this has been determined, a 'bottom-up' approach deserves preference: begin with the least invasive option, and then move 'up the ladder'. In children with severe problems, the non-invasive management options can be foregone if these are not expected to produce significant results; children with severe cognitive disorders, for instance, will likely not respond well to behavioral management.

An example of a potential treatment strategy is shown in figure 1, which is based on the results of this thesis. In summary, for posterior drooling a more aggressive approach is warranted because of the risk of aspiration pneumonias. We therefore recommend initial treatment with a combined parotid and submandibular injection with botulinum toxin. In the absence of a satisfactory response, 3- or 4-duct ligation (or gland extirpation) should be considered.

For isolated anterior drooling, a more cautious approach is often acceptable. Non-invasive management strategies, such as correction of situational factors (eg. posture), speech language therapy, behavioral therapy, or systemic anticholinergics can be considered first if the problem is not too severe. Failing these, invasive management in the form of botulinum toxin to the submandibular glands should be considered, and can be repeated if successful. If there is no clinically notable response to these injections, additional injection to the parotid glands can be attempted.

If there is still no clinically notable response, surgery is a potential option. In the case of non-progressive disease, submandibular duct relocation is the initial treatment of choice due to the wide experience, good efficacy, and low incidence of unwanted side effects (after the initial peri-operative period). In progressive disease, sub-mandibular duct relocation can increase the risk of future aspiration and should be avoided. Gland extirpation or duct ligation is recommended in such cases.

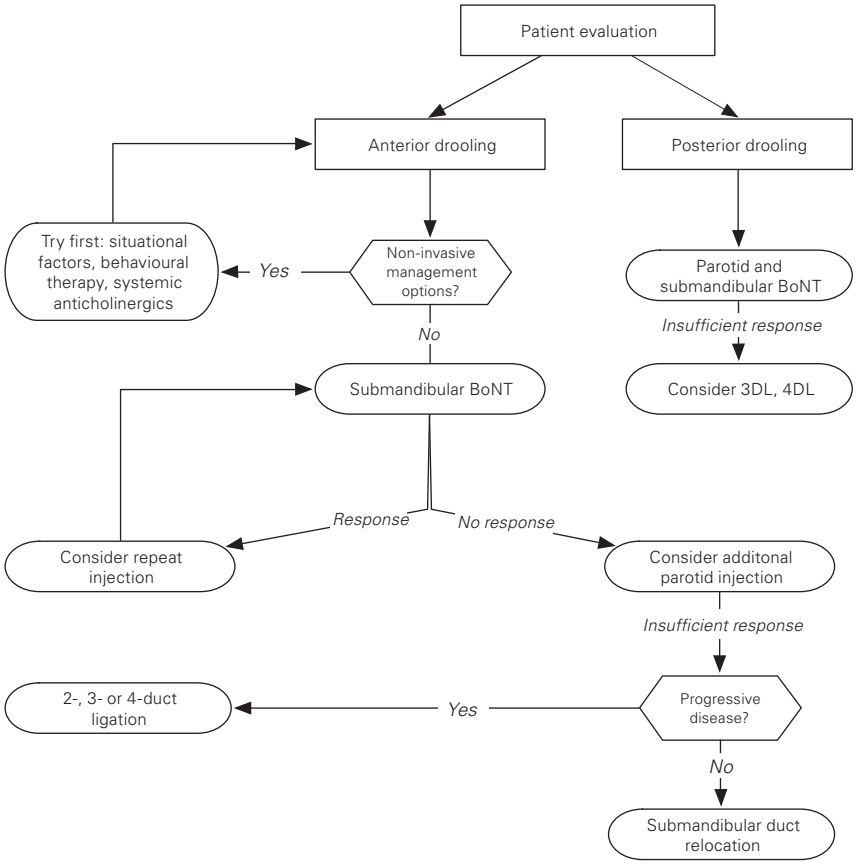

Figure 1 Possible treatment diagram for drooling in children.

FUTURE RESEARCH

In our view, future research should focus on three potential treatments: botulinum toxin, systemic anticholinergics, duct ligation, and the relative advantages and disadvantages of each.

For botulinum toxin the most important question is the efficacy of repeated injections. Are these useful? Are they useful in non-responders? And when should they be abandoned?

For systemic anticholinergics, the recent renewed interest means that there is a pressing need for more evidence, and for more information regarding their effectiveness compared to other treatments.

Duct ligation is, in our view, the most promising recent treatment for drooling in neurologically challenged children, and many questions regarding its application remain. How does it compare to submandibular duct relocation in (long-term) efficacy? How many ducts should be ligated? What causes treatment failure? And how does it compare to less invasive treatments such as botulinum toxin in both effectiveness and morbidity? Could it be a viable alternative to botulinum toxin?

As is often the case, much is yet to be learned.

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Chapter 9

Summary

Drooling that persists after the age of four years is commonly considered pathological and is usually a symptom of underlying neurological conditions such as cerebral palsy. Although frequently under-estimated, it is among the most common dysfunctions in children with cerebral palsy, affecting up to 58% of children and can have serious consequences for a person's well being. Some children are reported to consider it their worst affliction.

Humans produce 1-1.5 liters of saliva each day. The submandibular gland produces sixty-five to seventy percent of all saliva, and the parotid glands produce approximately twenty percent. Drooling generally occurs if an individual is insufficiently able to swallow the saliva produced. Potential causative factors include poor coordination of muscles in the oral stage of swallowing, infrequent swallowing and incomplete mouth and lip closure.

Anterior (visible) drooling often leads to a skin irritation and maceration on the chin and mouth. The constant presence of saliva can impair articulation and impair communication. In rare cases, there may be chronic loss of fluid and nutrients requiring treatment.

Perhaps even more serious are the associated social consequences. The unpleasant sight and odor can result in alienation from other members of society. Children can be excluded from certain activities and the stigma associated with drooling means that children are frequently underestimated with regards to their mental abilities. For parents caretakers, constant saliva loss can mean multiple daily bib or clothing changes, significantly increasing the burden of daily care. Damage to clothes, toys, furniture and electrical devices such as computers and communication aids have been reported.

Posterior drooling (aspiration) can lead to recurrent pneumonias, which in some cases require multiple intensive care admissions per year. The clinical morbidity of posterior drooling is high, and includes somatic, psychological and social problems. Many treatment options have been attempted for drooling over the years. There is no true consensus over the optimum treatment strategy, but it appears widely agreed that children should be evaluated by a multidisciplinary team to determine the best approach in a specific case.

The least invasive treatments include behavioral therapy, speech language therapy and correction of situational factors. Pharmacological therapy has focused on the reduction of saliva volume, which is mostly controlled by the parasympathetic nervous system. Most commonly, anticholinergic drugs that inhibit parasympathetic activity

have been prescribed. Administered systemically, however, these substances frequently lead to undesirable side effects.

Recently, the re-introduction of botulinum toxin has allowed for localized anticholinergic therapy. Injected into a salivary gland under general anesthesia, it inhibits parasympathetic activity and reduces the production of saliva for several months. Administration this way prevents the systemic side effects of previously used anticholinergics. Numerous studies since 2000 have shown the effectiveness and low morbidity of botulinum toxin for the reduction of drooling for a period of several months. It is now considered a first-line treatment when conservative measures fail.

Surgery has been a mainstay in the treatment of drooling for several decades. Although the most invasive, surgery is regarded to be among the most effective treatments for severe drooling. Initial treatments in the 1960s and 70s focused on rerouting the ducts of the parotid gland, submandibular gland removal and on surgical denervation techniques.

Since the 1980s, bilateral submandibular duct relocation (SMDR) with or without excision of the sublingual gland has arisen as the de-facto standard surgical technique. The procedure involves the rerouting of the submandibular ducts from the anterior oral cavity to the posterior oropharynx. As a result, saliva is more easily swallowed while still preserving a physiologically humid oral cavity and allowing unimpaired parotid gland function for mastication. Some surgeons additionally resect the sublingual glands to prevent ranula-formation. The procedure has a high reported rate of success (80%).

More recently, ligation of parotid or submandibular ducts has become the subject of increasing interest. This technique is reported to improve saliva handling and improve both anterior and posterior drooling. It is also easier to perform than submandibular duct relocation.

Despite the increase in available data, there is a paucity of controlled studies and of data that directly compares various treatments. The objective of this thesis is to provide further evidence for the various treatments of drooling, as well as their relative merit, to support the development of a universal treatment protocol. Specific research questions include:

- How effective is submandibular duct relocation for severe drooling, and what is the quality of the associated evidence? (chapter 2).
- What is the effect of botulinum toxin for drooling when employed on a larger scale, and how long do its effects last? (chapter 3)
- Which factors influence outcomes of botulinum toxin when used for severe drooling? (chapter 4)
- What is the relative effect of botulinum toxin versus submandibular duct relocation (chapter 5)?
- What is the relative effect of submandibular vs. parotid injections of botulinum toxin? (chapter 6)
- What is the effect of salivary duct ligation for anterior and posterior drooling? (chapter 7)
- What is the relative value of botulinum toxin and surgery in the management of drooling? (all chapters)

Chapter 1 is the introduction, described above.

Chapter 2 explores the literature on submandibular duct relocation in a systematic review, to establish the effect and quality of the evidence for this surgical technique. We performed searches on the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, PubMed and EMBASE. Titles and abstracts were reviewed, and the full text was retrieved of any article that potentially met eligibility criteria. The references of the retrieved articles were hand-searched for previously unfound studies. Relevant data regarding participants, interventions, outcome measures, follow-up duration, complications were collected. All included studies were critically appraised using a validated checklist, and only studies with a score of at least 50% on the critical appraisal were considered for data synthesis. We found a mean score for methodological quality of 38.4% (range: 21.4-67.9; SD 10.9). Four papers met the minimum methodological criteria set. Each described a success percentage of more than 50%. Unfortunately, meta-analysis of efficacy was not possible due to differences in outcome assessment. An overall complication of 8.7% was found; floor-of-mouth or tongue swelling (2.2%), post-operative hemorrhage (2.7%) and ranulas (3.2%) were most commonly reported. We conclude that, although there is a large amount of favorable experience with submandibular duct relocation, there is relatively little formal evidence for its efficacy.

Chapter 3 is a prospective study to establish the effect of botulinum toxin injected into the submandibular glands, and the duration of this effect. A prospective cohort of 131 children with cerebral palsy and moderate to severe drooling was formed.

Systematic follow-up measurements were collected before, 8 weeks after, and 32 weeks after treatment. Evaluation of the severity of drooling was done through the direct-observational drooling quotient (DQ; yields a score of 0-100, with 100 corresponding to severe continuous drooling). Additionally, parents were asked to score the severity of drooling during the previous two weeks using a visual analogue scale (VAS; yields a score of 0-100, with 100 corresponding to severe drooling). Response to treatment was defined as a 50% reduction in DQ.

A clinically notable response was found in 47% of children, reflected in a significant mean reduction in DQ from a baseline of 29 to 15 after 8 weeks and 19 after 32 weeks (P<.001; 2-sided paired t-test). The mean VAS score decreased from 80 at baseline to 53 after 8 weeks and increased to 66 after 32 weeks (P<.001; 2-sided paired t-test). Kaplan-Meier analysis showed that patients who initially responded to treatment experienced relapse after a median of 22 weeks (interquartile range, 20-33 weeks). We conclude that botulinum toxin injection in the submandibular glands is effective for treatment of drooling in approximately half of patients for a median of 22 weeks.

Chapter 4 investigates if the different responses to submandibular botulinum toxin can be explained by variations in dysfunctions in different cerebral palsy subtypes. We investigated treatment response in 80 spastic and 48 dyskinetic children. Additionally, 28 fully ambulant children with only mental disability were examined. The primary outcomes were the drooling quotient, as well as parotid and submandibular flow rates (measured via cotton rolls placed at the duct openings). Both the DQ and submandibular flow rates decreased following treatment. Ninety-three children showed a reduction of more than 50% in DQ, or more than 30% in submandibular flow. Notably, children who showed a clinically relevant response to injection also showed a reduction in parotid flow (even though this was not injected). In all three subgroups, non-responders showed an increase in parotid flow. We hypothesize that treatment failure is a result of increased parotid flow, potentially due to inadequate inhibition of the reflex arc of salivary secretion. We were unable to identify factors that can predict which children respond to botulinum toxin before treatment.

Chapter 5 is an analysis of the effect of parotid injection versus submandibular injection of botulinum toxin, to determine if parotid or combined injection is more effective than submandibular injection alone. We prospectively recruited twenty-one children, of which nineteen were available for study (9 boys and 8 boys). Children were initially treated with submandibular injection alone, and were evaluated before the injection and 8 weeks thereafter (DQ and VAS). Overall,

submandibular injection led to a significant reduction in DQ (from baseline of 26 to 16 after 8 weeks; P=0.05, 2-sided paired *t*-test) and VAS (from baseline of 80 to 51 after 8 weeks; P<0.001, 2-sided paired *t*-test). Ten children did not show a significant response to submandibular injection, defined as a reduction of 50% in DQ and 30% in VAS. Eight of these 'treatment failures' underwent additional parotid injection. Injection of the parotid gland led to a mean reduction in DQ from a baseline value of 20 to 8 (P=0.007). The VAS showed an improvement from 78 to 45 after parotid injection (P=0.03). Four children could subsequently be qualified as 'responders' to treatment. We conclude that additional injection of parotid injection can increase response to botulinum toxin from 47% to 68%.

Chapter 6 is a comparison of botulinum toxin versus submandibular duct relocation in patients who have undergone both treatments. A within-participants study was performed in nineteen children and young adults (10 boys, nine girls; mean age 11 years 5 months) with cerebral palsy or non-progressive developmental delay. All participants initially underwent submandibular injections with botulinum toxin. At least six months later, submandibular duct relocation was performed. The primary outcome was the DQ, measured before each intervention and 8 and 32 weeks thereafter. A multivariate analysis of variance of repeated measures was performed, with the measurement points as the within-participant variables. We found that surgery led to a greater improvement in DQ than botulinum toxin (Hotelling's trace: F=11486; repeated measures ANOVA). After botulinum toxin, the DQ fell from a baseline value of 30 to 18 after 8 weeks (p=0.02; 2-sided paired *t*), and rose to 22 after 32 weeks (p=0.05; 2-sided paired *t*). Surgery led to a reduction in DQ from a baseline of 28, to 10 after 8 weeks (p<.001; 2-sided paired *t*) and 4 after 32 weeks (p<.001; 2-sided paired *t*). We investigated the possibility of selection bias by comparing patient characteristics and treatment response to botulinum toxin in this group of children to the ones in Chapter 3. No significant differences were found. We conclude that submandibular duct relocation provides a larger and longer-lasting effect than submandibular botulinum toxin.

Chapter 7 is a case series of duct ligation for severe anterior and posterior drooling. Twenty-one children were included (14 boys, 9 girls; mean age 13 years, 7 months). Sixteen were diagnosed with cerebral palsy, 3 non-progressive neurological disorder, and 2 a progressive neurological disorder. Fifteen children were treated with bilateral submandibular duct ligation (2-duct ligation, 2DL), three with ligation of both submandibular ducts and a parotid duct (3-duct ligation, 3DL) and five with ligation of both submandibular and both parotid ducts (4-duct ligation, 4DL). Children were evaluated before treatment, 8 weeks after treatment, and 32 weeks after treatment. Primary outcomes were the DQ, VAS and incidence of pneumonias.

Duct ligation led to significant objective and subjective improvement in anterior drooling (Hoteling's trace F=10808; repeated measures ANOVA). The DQ fell from a baseline value of 27 to 8 after 8 weeks (P=0.001) and 12 after 32 weeks (P=0.06). The VAS fell from 85 to 48 (P=0.001) after 8 weeks and to 52 after 32 weeks (P=0.003). Although duct ligation appeared to reduce the number of aspiration pneumonias in posterior drooling, no statistical significance was found (P=0.23). We conclude that duct ligation has a significant short-term effect on anterior drooling.

Chapter 8, the general discussion, summarizes the outcomes of the studies. We conclude that both botulinum toxin and two surgical methods are effective treatments of drooling, and are relatively well tolerated. Botulinum toxin has very little complications and works quickly. It is a useful first step 'more than conservative treatment' is required. Additional injection of the parotid glands can improve treatment response. We are still not able to successfully predict which patients will respond to treatment, and which will fail. There is also insufficient information on the effect of repeated injections.

Submandibular duct relocation appears more effective than botulinum toxin, and provides a 'definitive' solution. The main significant disadvantages of the procedure are the operative time (approximately 2 hours), peri-operative risks and morbidity. As a result, surgery is not infrequently postponed until all other avenues have been explored, which means that children might be undertreated in the meantime.

Salivary duct ligation showed promise to address this dilemma. Although our initial results confirm its effectiveness, treatment response appears to be slightly worse than to submandibular duct relocation. Furthermore, a larger number of children have required renewed surgery due to early or late treatment failure. However, as the morbidity of the initial procedure is so much lower for duct ligation, it is nonetheless possible that the overall morbidity/efficacy-ratio is better for duct ligation than for submandibular duct relocation.

We propose that physicians looking to treat children with drooling should implement a solid method of evaluation. We also think that a multidisciplinary approach is advisable. If there is no significant posterior drooling, children should initially be treated with the least invasive method that can reasonably be expected to be effective.

Finally, several potential subjects of future discussion are proposed.

Chapter 10

Nederlandstalige samenvatting

Kwijlen dat persisteert boven de leeftijd van vier jaar wordt als pathologisch beschouwd, en is in de regel een gevolg van onderliggende neurologische problematiek zoals een cerebrale parese. Hoewel deze klacht vaak wordt onderschat, behoort het tot de meest voorkomende dysfuncties waarmee kinderen met cerebrale parese geconfronteerd worden. Tot 58% van de kinderen lijdt in meer of mindere mate aan kwijlen, met vaak grote gevolgen voor het welzijn. Sommige kinderen beschouwen het hun ernstigste handicap.

Mensen produceren 1-1,5 liter speeksel per dag. De twee glandulae submandibulares zijn verantwoordelijk voor 65-70% van het geproduceerde speeksel, en de glandulae parotides voor circa twintig procent. Kwijlen treedt op als iemand onvoldoende in staat is om het geproduceerde speeksel weg te slikken. Tot de oorzaken bij cerebrale parese behoort onder meer slechte mondmotoriek, infrequent slikken en onvolledige mond- en lipsluiting.

Anterieur (zichtbaar) kwijlen leidt frequent tot irritatie en wondjes op de huid rond de mond en kin. De constante aanwezigheid van speeksel kan de articulatie storen en communicatie bemoeilijken. In bepaalde gevallen kan er dermate verlies zijn van vocht en voedingsmiddelen dat behandeling nodig is.

Wellicht nog ingrijpender zijn de begeleidende sociale gevolgen. De onaangename aanblik en geur van het speeksel kan leiden tot vervreemding van de maatschappij. Kinderen worden soms buitengesloten van sociale activiteiten, en het stigma dat geassocieerd is met het speekselverlies leidt vaak tot onderschatting van de mentale capaciteiten van een kind. Voor ouders en verzorgers kan het voortdurend speekselverlies betekenen dat kinderen per dag meerdere malen volledig verkleed en verschoond moeten worden, hetgeen een grote belasting is. Tenslotte wordt schade aan kleding, speelgoed, interieur en electronische apparaten zoals computers en communicatiehulpmiddelen gemeld.

Posterieur kwijlen (aspiratie) kan leiden tot recidiverende pneumonieën (long-ontstekingen), waarvoor in sommige gevallen jaarlijks meerdere opnames op een intensive care nodig zijn. De klinische morbiditeit is ernstig, en omvat zowel somatische als psychologische en sociale problemen.

Er zijn veel behandelingen geprobeerd voor kwijlen. Desalniettemin bestaat er geen goede consensus over de optimale behandelstrategie. De meeste experts lijken het er wel over eens dat evaluatie door een multidisciplinair team de voorkeur geniet.

De minst ingrijpende behandelingen zijn gedragstherapie, logopedie en correctie van omgevingsfactoren. De farmacologische therapie is voornamelijk gericht op het terugbrengen van de speekselproductie, die voornamelijk onder parasympathische invloed staat. Meestal worden systemische anticholinergica voorgeschreven, die de parasympathische activiteit verminderen. Deze gaan echter niet zelden gepaard met bijwerkingen.

In de afgelopen tien tot vijftien jaar heeft de herintroductie van botulinetoxine de mogelijkheid van lokale anticholinerge therapie geboden. Botulinetoxine kan (meestal in narcose) in de speekselklier worden geïnjecteerd en leidt zo tot een chemische denervatie. De speekselproductie wordt hiermee gedurende enkele maanden geremd zonder de bijwerkingen van systemische anticholinergica. Diverse studies hebben aangetoond dat dit een effectieve behandeling is met weinig bijwerkingen. Botulinetoxine wordt nu gezien als een eerste behandeling als conservatieve maatregelen onvoldoende effect hebben.

Chirurgische interventies vormen al decennia een hoeksteen in de behandeling van kwijlen. Hoewel chirurgie het meest ingrijpend is, wordt het algemeen beschouwd als de meest effectieve en permanente oplossing. De eerste operaties in de jaren 60 en 70 van de vorige eeuw bestonden vooral uit het verwijderen van de glandula submandibularis, het verplaatsen van de ductus parotides en op het chirurgisch onderbreken van de innervatie van de grote gepaarde speekselklieren.

Sinds de jaren 80 is bilaterale submandibulaire ductusrelocatie de de-facto standaardingreep. Hierbij worden de afvoergangen (ducti) van de glandulae submandibularis verplaatst van hun anatomische positie vooraan in de mond naar de tongbasis. Het speeksel kan hierdoor makkelijker worden weggeslikt, terwijl een fysiologisch vochtige mondholte en ongestoorde parotisfunctie behouden blijven. Sommige chirurgen verwijderen gelijktijdig de glanduale sublinguales om de vorming van ranula's te vermijden. De procedure kent een gerapporteerd succespercentage van 80%.

Recentelijk is de chirurgisch onderbinden (ligeren) van de ducti parotides of submandibulares in opkomst. Deze techniek is technisch eenvoudiger en zou leiden tot vermindering van zowel anterieur als posterieur kwijlen.

Hoewel de afgelopen jaren veel nieuwe informatie is verschenen, blijft er een gebrek aan gecontroleerde studies, en met name aan gegevens die direct de verschillende behandelmogelijkheden vergelijken. Dit proefschrift is bedoeld om aanvullend bewijs te vinden voor de verschillende behandelmodaliteiten, alsmede

hun onderlinge effectiviteit. Het doel is om uiteindelijk te komen tot een universeel ontwikkelingsprotocol. Specifieke onderzoeksvragen zijn:

- Hoe effectief is submandibulaire ductusrelocatie voor ernstig kwijlen, en hoe goed is het beschikbare bewijs? (hoofdstuk 2)
- Wat is het effect van botulinetoxine voor kwijlen, en hoe lang houdt dit stand? (hoofdstuk 3)
- Welke factoren beïnvloeden de uitkomst van botulinetoxine? (hoofdstuk 4)
- Wat is het relatieve effect van botulinetoxine versus submandibulaire ductusrelocatie? (hoofdstuk 5)
- Wat is het relatieve effect van injecties van botulinetoxine in de glandula submandibularis en parotis? (hoofdstuk 6)
- Hoe effectief is ductusligatie in het verminderen van anterieur en posterieur kwijlen? (hoofdstuk 7)
- Wat is de relatieve waarde van botulinetoxine en chirurgie bij de behandeling van kwijlen (alle hoofdstukken)

Hoofdstuk 1 is de introductie, hierboven beschreven.

Hoofdstuk 2 is een systematische literatuurstudie naar submandibulaire ductusrelocatie. De Cochrane Database of Systematic Review, Cochrane Central Register of Controlled Trials, PubMed en EMBASE werden doorzocht en relevant artikelen gescreend op titel en samenvatting. Potentieel relevante artikelen werden volledig bestudeerd, en referenties werden handmatig doorzocht voor aanvullende studies. Relevante data met betrekking tot studiedeelnemers, interventies, uitkomstmaten, follow-upduur en complicaties werden verzameld. Alle geïncludeerde studies werden beoordeeld met behulp van een gevalideerde vragenlijst. Alleen studies met een methodologische score van tenminste 50% werden acceptabel beschouwd. De gemiddelde methodologische kwaliteit was 38.4% (bereik: 21.4-67.9, SD 10.9). Vier artikelen voldeden hieraan, en elk beschreef een succespercentage van meer dan 50%. Helaas was meta-analyse van de effectiviteit niet uit te voeren door een grote variatie in uitkomstmaten. Het percentage complicaties bedroeg 8.7% Voor mondbodemzwelling (2.2%), nabloedingen (2.7%) en ranulavorming (3.2%) werden beschreven. We concluderen dat de ervaring met submandibulaire ductusrelocatie gunstig is, maar dat er relatief weinig formeel bewijs is voor de effectiviteit ervan.

Hoofdstuk 3 is een prospectieve studie naar het effect van botulinetoxine-injectie in de glandulae submandibularis, en de duur van dat effect. 131 kinderen met cerebrale parese en matig tot ernstig kwijlen werden vervolgd. Kinderen werden

systematisch geëvalueerd vóór behandeling, en 8 en 32 weken daarna. De ernst van het kwijlen werd gekwantificeerd door middel van het drooling quotiënt, een direct-observationele meetmethode (DQ; geeft een score van 0-100 waarbij '100' correspondeert met zeer ernstig, voortdurend kwijlen). Daarnaast werd de subjectieve ernst van het kwijlen in de twee voorafgaande weken aangegeven door ouders middels een visueel-analoge schaal (VAS; geeft een score van 0-100 waarbij '100' correspondeert met zeer ernstig, voortdurend kwijlen). Behandelrespons werd gedefinieerd als een vermindering van 50% van het DQ.

47% van de kinderen toonden een dergelijke behandelrespons. Het gemiddelde DQ daalde van een uitgangswaarde van 29 naar 15 na 8 weken en 19 na 32 weken ($P<0.001$; 2-zijdig gepaarde t-toets). De gemiddelde VAS daalde van een uitgangswaarde van 80 naar 53 na 8 weken en 66 na 32 weken ($P<0.001$; 2-zijdig gepaarde t-toets). Kaplan-Meier analyse toonde dat de mediane duur van de respons op botulinetoxine 22 weken was (interkwartielbereik: 20-33 weken). We concluderen dat botulinetoxine bij circa de helft van de patiënten effectief is, gedurende een mediane periode van 22 weken.

Hoofdstuk 4 onderzoekt of het verschil in respons op submandibulaire botulinetoxine verklaard kan worden door variaties in de dysfuncties die optreden bij de verschillende subtypen van cerebrale parese. Tachtig spastische en 48 dyskinetische kinderen werden onderzocht, evenals 28 ambulante kinderen met enkel een mentale beperking. De primaire uitkomsten waren het DQ, en de flowrate van de glandulae submandibulares en parotides (gemeten met behulp van wattenrollen). 93% van alle kinderen toonden een respons, gedefinieerd als een reductie van 50% van het DQ óf 30% van de submandibulaire flowrate. Opmerkelijk genoeg nam bij de kinderen die behandelrespons vertoonden, ook de parotisflowrate af. Non-responders in alle subgroepen toonden juist een verhoogde parotisflow. We hypothetiseren dat non-response een gevolg is van inadequate centrale inhibitie van de speekselsecretie. De studie biedt ons geen aanknopingspunten om de respons vóór behandeling bij een individueel kind te voorspellen.

Hoofdstuk 5 is een vergelijking tussen het effect van injectie van botulinetoxine in de glandula parotis en submandibularis, om te beoordelen of de behandelrespons verbeterd kan worden door middel van gecombineerde injecties. 21 kinderen werden prospectief geïncludeerd, waarvan er 19 beschikbaar waren voor analyse (9 meisjes en 8 jongens). De primaire uitkomstmaat waren het DQ en VAS, gemeteen in de uitgangssituatie en 8 weken na behandeling. Alle kinderen werden initieel behandeld met een injectie in de glandula submandibularis. Dit leidde tot een significante reductie in DQ (van uitgangswaarde 26 naar 16 na 8 weken;

P=0.05, 2-zijde gepaarde t-toets) en VAS (van uitgangswaarde 80 naar 51 na 8 weken; P<.001; 2-zijdig gepaarde t-toets). Tien kinderen hadden geen klinisch significante reductie op botulinetoxine (gedefinieerd als 50% afname van DQ én 30% afname van VAS). Acht hiervan kregen een aanvullende injectie in de glandula parotis beiderzijds. Injectie van de parotis leidde tot een gemiddelde afname van het DQ van een uitgangswaarde van 20 naar 8 (P=0.007). De VAS verbeterde van 78 naar 45 na parotisinjectie (P=0.03). Vier extra kinderen konden als 'responders' beschouwd worden. We concluderen dat aanvullende injectie van de glandula parotis zinvol is, en het responspercentage kan doen toenemen van 47% naar 68%.

Hoofdstuk 6 is een vergelijking van submandibulaire ductusrelocatie met injectie van botulinetoxine in de glandula submandibularis. Een 'within-subjects' studie werd uitgevoerd in 19 kinderen, waarin elke deelnemer zijn eigen controle was. Tien jongens en negen meisjes werden geïncludeerd met cerebrale parese of niet-progressieve ontwikkelingsachterstand (gemiddelde leeftijd 11 jaar en 5 maanden). Alle deelnemers ondergingen aanvankelijk behandeling met submandibulaire botulinetoxine, gevolgd door submandibulaire ductusrelocatie ten minste zes maanden later. De primaire uitkomst maat was de DQ, gemeten in de uitgangssituatie en 8 en 32 weken na elke interventie. Een multivariate variantie-analyse van herhaalde metingen werd uitgevoerd, met de meetmomenten als de 'within-subject' variabelen. We vonden dat chirurgie een groter effect heeft dan submandibulaire botulinetoxine (Hotelling's trace F=11486). Na toediening van botulinetoxine nam het DQ af van een uitgangswaarde van 30 naar 18 na 8 weken (p=0.02; 2-zijdig gepaarde t-toets). Na 32 weken bedroeg de DQ 22 (p=0.05; 2-zijdig gepaarde t-toets). Submandibulaire ductusrelocatie leidde tot een afname van het DQ van 30 tot 10 na 8 weken (P<0.001; 2-zijdig gepaarde t-toets) en 4 na 32 weken (P<0.001; 2-zijdig gepaarde t-toets). Analyse toonde geen aanwijzingen voor selectiebias, veroorzaakt door het feit dat bijvoorbeeld alleen 'slechte' responders op botulinetoxine waren geïncludeerd; de resultaten van botulinetoxine in deze groep waren vergelijkbaar met die in hoofdstuk 3. We concluderen dat submandibulaire ductusrelocatie een groter en langer aanhoudend effect heeft dan botulinetoxine.

Hoofdstuk 7 is een 'case series' waarin ductusligatie wordt beschreven voor anterieur en posterieur kwijlen. 21 kinderen werden geïncludeerd, 14 jongens en 9 meisjes (gemiddelde leeftijd 13 jaar en 7 maanden). Zestien hadden cerebrale parese, drie niet-progressieve neurologische problemen, en 2 een progressief neurologisch beeld. Vijftien kinderen werden behandeld door middel van het onderbinden (ligeren) van de ductus submandibularis beiderzijds (2-ductligatie, 2DL), drie door middel van het onderbinden van de ductus submandibularis

beiderzijds én één ductus parotides, en vijf door middel van onderbinding van zowel de ductus submandibularis als parotis beiderzijds. De primaire uitkomstmaten waren het DQ, de VAS en het aantal aspiratiepneumonieën. Ductusligatie leidde tot een duidelijke verbetering van het anterieure kwijlen (Hotelling's trace F=10808; repeated measures ANOVA). Het DQ nam van een uitgangswaarde van 27 af naar 8 na 8 weken (P=0.001; 2-zijdig gepaarde t-toets) en 12 na 32 weken (P=0.06). De VAS nam af van 85 naar 48 na 8 weken (P=0.001; 2-zijdig gepaarde t-toets) en 52 na 8 weken (P=0.003). Hoewel het aantal aspiratiepneumonieën leek af te nemen, was dit niet statistisch significant (P=0.23). We concluderen dat ductusligatie op de korte termijn een significant effect heeft op anterieur kwijlen.

Hoofdstuk 8, de discussie, bevat een samenvatting van de studies. We concluderen dat zowel botulinetoxine als de onderzochte chirurgische technieken effectieve behandelingen zijn van kwijlen. De morbiditeit van beide ingrepen is beperkt. Botulinetoxine heeft weinig complicaties en werkt snel. Het is een zinvolle eerste farmacologische of invasieve behandeling. Aanvullende injectie van de parotisklieren kan het effect versterken. We zijn nog niet in staat om de respons op behandeling van tevoren te voorspellen. Er is ook nog onvoldoende informatie over het effect van herhaalde injecties.

Submandibulaire ductusrelocatie lijkt effectiever dan botulinetoxine, en biedt een 'definitieve' oplossing. De belangrijkste nadelen van de ingreep zijn de operatieduur (circa 2 uur), en de bijkomende operatierisico's en morbiditeit. Dit leidt er toe dat chirurgisch ingrijpen vaak nog wordt uitgesteld, en brengt het risico met zich mee dat kinderen worden onderbehandeld.

Ductusligatie is een veelbelovende oplossing voor dit dilemma. Hoewel onze initiële resultaten de effectiviteit van de ingreep bevestigen, lijkt het effect wat minder dan van submandibulaire ductusrelocatie. We hebben bovendien gemerkt dat in relatief veel gevallen op termijn een hernieuwde ingreep nodig bleek. De zeer geringe morbiditeit van ductusligatie betekent echter dat de totale morbiditeit van de ingreep op macroniveau nog wel eens gunstiger zou kunnen zijn dan die van submandibulaire ductusrelocatie.

We vinden dat artsen die deze problematiek willen behandelen in ieder geval een robuuste methode moeten hebben om de kinderen te evalueren en het effect van behandeling te vervolgen. Het beste gebeurt dit in een multidisciplinair overleg. Als er geen aspiratie is, zouden kinderen initieel behandeld moeten worden met de minst invasieve methode waarvan redelijkerwijs effect verwacht kan worden.

Als laatste worden nog enkele potentiële toekomstige onderzoeksgebieden voorgesteld.

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Curriculum Vitae

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CURRICULUM VITAE

Anthonius Roderick Theodoor (Arthur) Scheffer werd op 18 augustus 1983 geboren in Utrecht. Zijn initialen maakten het eigenlijk bij voorbaat al duidelijk dat hij in de medische wereld terecht zou komen. Hij groeide op in Oss en vermaakte zich in zijn jeugd onder anderen met voetbal, gitaarspelen, auto's en zeilen. Na succesvolle afronding van zijn gymnasiumopleiding begon hij in 2001 met een volle bos blonde krullen aan de studie Geneeskunde aan de Radboud Universiteit Nijmegen. Tijdens zijn studie werkte hij als telemarketeer bij de inmiddels failliete DSB bank. Daarnaast was hij vanwege zijn affiniteit met informatietechnologie werkzaam als redacteur bij de elektronica- en technologiewebsite Tweakers.net (hij wordt nog steeds beschouwd als één van de originele Apple-aanhangers). Hij liep stage in het KCMC in Moshi te Tanzania, waar hij in februari 2014 zijn rentree maakte voor de non-profit organisatie AfriKNO.

Zijn voorliefde voor de Keel-, Neus- en Oorheelkunde ontstond tijdens zijn studie en kwam tot uiting in een wetenschappelijke stage naar de behandeling van ernstig kwijlen. Dit vormde de opmaat tot het promotieonderzoek dat dit proefschrift tot gevolg had en was de sleutel tot een opleidingsplaats tot KNO-arts. Bovendien werden subsidies van het Johanna Kinderfonds, Adriaan Kinderfonds en Phelps Stichting binnengehaald hetgeen het voortbestaan van de onderzoekslijn verzekerde. Gedurende zijn opleiding zette Arthur zich als voorzitter van de OOR-ON Arts-assistentenvereniging Nijmegen in voor regionaal discipline- overstijgend onderwijs en was hij assistentlid bij het regio-overleg van de OOR-ON. Zijn interesse in management werd nog eens onderstreept door het volgen van de prestigieuze 'Leergang management en bestuur voor jonge zorgprofessionals'.

In december 2014 zal hij zijn opleiding tot KNO-arts voltooien.