Clinical aspects of drooling in children with Cerebral Palsy

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Contents

Chapter 1

General introduction

Cerebral palsy (CP) is the most frequent cause of physical disability in children and can be defined as a disorder of aberrant control of movement and posture, appearing early in life (before the first birthday) secondary to a non progressive CNS lesion. The worldwide prevalence of CP is approximately 2 to 2.5 per 1000 live births.[1] Common additional impairments are sensory dysfunction (seeing, hearing), cognitive and behavioral deficits, and dysfunctional oral motor control hampering the ability of a child to realize his or her intrinsic developmental potential. Although not precisely established, one out of three individuals with CP drools to some extent. Drooling contributes heavily to the burden in children with CP and social alienation they experience.[2,3] During recent years there is increasing evidence that children who drool might benefit from behavioral modifying therapy[4] or from more invasive techniques like ultrasound-guided Botulinum Toxin type A injections (BoNT-A) into the submandibular glands[5] or surgery.[6] Research is now focused on refining the drooling therapy and on evaluation of the efficacy of the different interventions. An outline of these findings will provide the clinician with essential information on which a rational treatment strategy can be based.

Aims and Study design

The principal objective of this thesis is to refine ultrasound-guided submandibular BoNT-A injection to treat drooling and to provide basic concepts for the mechanisms that underlie the drooling problem. Therefore, a prospective cohort study was performed in 151 Dutch children with either CP or with exclusively 'intellectual disability'.

All *participants* were screened in the outpatient drooling clinic at the Radboud University Nijmegen Medical Centre, The Netherlands between February 2000 and March 2010.

Inclusion criteria: children aged 3–19 years (male and female); confirmed diagnosis of cerebral palsy or exclusively mental disability (medical history, neurological examination, magnetic resonance imaging (MRI), electroencephalography); score of ≥ 3 on drooling severity and frequency scale[7] (indicating moderate to profuse drooling); informed consent from parents/caregivers.

Exclusion criteria: progressive neurological condition; enrolment in another medical study; previous surgical procedure for saliva control; use of drugs that

interfere with saliva secretion (anticholinergic and neuroleptic drugs, benzo-diazepines).

The mean age of the children was 10 years/ten months with a Standard Deviation (SD) of 4 years/10 months. Most of the children with CP were non-ambulatory and 70% of them had an Intelligence Quotient (IQ) below 70. All children with intellectual disabilities were ambulatory, and also had an IQ below 70.

Procedures. An ultrasound-guided injection of BoNT-A was given bilaterally into the submandibular salivary glands. A total dose of up to 50 U Botox® (Allergan B.V., Nieuwegein, The Netherlands) was used.

Scoring. Both, drooling intensity and salivary flow were measured at baseline, 8 weeks and 32 weeks after injection. Drooling intensity was evaluated using the drooling quotient (DQ). a semi quantitative observational method (expressed as a percentage). The DQ was scored according to the original design by recording all episodes of drooling during 10 minutes, while watching TV. A drooling episode was defined as new saliva being present on the lip margin or dripping from the chin. The presence or absence of drooling was assessed every 15 seconds (40 observations in 10 minutes).[8]

To measure the salivary flow rate the swab test is used: after drying the oral cavity with sterile gauze, three absorbent dental cotton rolls (Salivette®; Sarstedt B.V., Etten-Leur, The Netherlands) were placed in the oral cavity for a 5 minute-period: below the tongue in front of the orifices of the submandibular and sublingual glands as well as in the upper vestibules at the openings of the parotid ducts. The roll under the tongue and the two upper vestibules-rolls were weighted separately to be defined as submandibular and parotid flow. The increase in weight during the 5-minute period was converted into milliliters of saliva per minute to determine salivary flow rate.[9]

Primary Outcome Measures: Success to therapy was defined as a 30% submandibular flow reduction and/or a 50% reduction in DQ compared to baseline. The 30% demand has been previously reported and is explained by the estimated measurement error of the swab method to evaluate the salivary flow rate.[9]

Earlier it has been successfully stated that a 50% reduction in the Drooling Quotient reflects a clinical relevant change.[5] The submandibular glands, in fact the combined saliva of the submandibular and sublingual glands, produce about 60 to 70% of baseline salivary flow in the situation a person does not eat or drink.

In the event the Drooling Quotient is reduced by 50% following Botulinum Toxin injections the change of flow from the submandibular glands, being the only gland exposed to this intervention, must have added substantially to this reduction. A caretaker visual analog scale (VAS) score reflecting the severity of drooling over the previous 2 weeks served as secondary outcome measure. After receiving specific instructions, caretakers were asked to mark the extent of drooling on a 10-cm line. The VAS score was obtained by measuring the position of the mark in millimeters from the left end of the scale on a scale ranging from 0 to 100, the latter representing severe drooling. A change of 2 SD reduction compared to the baseline VAS score was considered clinically significant.[10]

Outline of this thesis

This thesis is divided into three sections. The first section, **chapter 2,** gives an overview how dysfunctional neuronal networks of swallowing contribute to a neglected clinical problem: the basic concepts of drooling. The impaired cerebral neuronal network in cerebral palsy is presented as a clinical model to illustrate a comprehensive framework considerate as crucial to coordinate oral sensorimotor functions along with associated upper and lower gastrointestinal functions. The deleterious clinical consequences of disturbances of this conceptual framework are discussed. Generally, it has been accepted that dysfunctional oral motor function plays a central role in drooling. **Chapter 3** presents a case–control study to determine whether excessive saliva production in drooling children diagnosed with CP exists and might be a cofactor. We also hypothesize that saliva secretion in children with dyskinetic CP might be increased because of the added mechanical stimulation of the salivary glands as a result of hyperkinetic oral movements.

In the second section, we present the re-evaluation of the efficacy of BoNT-A therapy for drooling. After the first report on BoNT-A as being an alternative, minimally invasive treatment for drooling, several studies have been published on this treatment. As we have been treating children in our multidisciplinary outpatient drooling clinic since 1999 we have build up a large experience on this subject. As the effectiveness being demonstrated, we became more interested in the efficacy and duration of the effect of BoNT-A when used on a large scale in clinical

practice. We report about our experience after treating 131 children with submandibular BoNT-A in **chapter 4.** Earlier drooling treatment results showed that up to 30 % of patients did not respond to submandibular injection of BoNT-A if response was defined as a 30% reduction of submandibular salivary flow in combination with a 50% reduction of the Drooling Quotient (DQ).[5,11] Given the number of non-responders, further research necessitates to search for factors that cause therapy failure. Currently, there is no agreement about what child characteristics will distinguish between a "successful" or "unsuccessful" therapy response after submandibular BoNT-A injections. After completing a thorough literature study, we identified that the following factors are suggested to contribute to drooling severity: head position, lip seal, voluntary control of tongue movements, control of voluntary movement functions, and mental age. In **chapter 5** we explore whether motor performance contributes to therapy outcome, and **chapter 6** describes the first attempt to reveal the contribution of head position, tongue protrusion, lip seal, voluntary tongue control, developmental age, control of voluntary movements, dysarthria and dysphagia (as defined by the International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY)) to the outcome of submandibular BoNT-A for drooling. Meanwhile, we observed in some children salivary thickening and increased feeding, speech and swallowing problems after submandibular BoNT-A. In view of the anticholinergic properties of BoNT, it is likely that the watery component of saliva will be reduced and that the salivary viscosity will increase post-BoNT. Therefore, we assumed that the sticky saliva might cause the swallowing problems due to increased protein concentrations and changed salivary viscosity causing more friction.[12] In **Chapter 7** we report on this experience and describe the increased risk of swallowing problems due to thickening of saliva after effective management with submandibular BoNT-A injections.

The importance to establish the impact of drooling and its treatment on health and quality of live is stressed in the last section. Given the costs of BoNT-A and the fact that BoNT has to be repeatedly applied, while needing aesthesia in children, it is important to formulate strict indications for this therapy. **Chapter 8** reports on an international Botulinum Toxin Therapy consensus statement for drooling, and hopefully assists the clinicians with the assessment, intervention and management of children and adults with drooling. **Chapter 9** summarises the main findings of this thesis and presents suggestions for future clinical research.

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Part

2

Chapter

Basic concepts of drooling

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Abstract

Defective swallowing and subsequent excessive drooling are substantial problems in a large number of neurologically affected individuals. As treatment of the underlying disorder often lacks, treatment of symptoms to maintain quality of life is worthwhile. The current review focuses on disturbed regulation of swallowing that leads to dysphagia and drooling, and integrates the accumulating evidence about functional and spatial distinct brain regions involved in swallowing. Cerebral Palsy is used as a clinical model to illustrate the comprehensive framework crucial for coordinating oral motor and associated gastrointestinal functions, and to discuss the deleterious clinical consequences of disturbances of this framework. At an early stage, particular note should be made to the important contribution of dysphagia and drooling to the burden of the child and his/her family. The formulation of rational prognostic statements of dysphagia is based on awareness of the topographic brain injury.

Search strategy and selection criteria

Members of the Multidisciplinary Outpatient Drooling Clinic at the Radboud University Nijmegen Medical Centre in The Netherlands continually review literature on dysphagia and drooling in neurologically affected patients. References for this review were obtained from personal reprint files, supplemented by Pub Med searches, with varying search periods (from 2005 to February 2011). The search terms "drooling", "saliva", "sialorrhea", "swallowing", "dysphagia", "cerebral palsy", "children", "brain regions", "autonomic", "fMRI", and "therapy" were used. Only English language articles were included. The final reference list was generated based on originality and relevance to the topics covered in the review.

Neural control of swallowing

Normal swallowing is a goal-directed sequential behaviour that requires the coordinated action and inhibition of the muscles located bilaterally around the oropharynx and oesophagus. The swallowing process is controlled in a complex manner involving the brainstem as well as cortical and subcortical central pathways. In addition, it requires a higher level of fine-tuning between the central circuits and the enteric nervous systems (ENS).

Accurate swallowing is dependent on sensory input from the oropharynx triggering bilateral afferents in specific regions of the trigeminal sensory nuclei. Subsequently, the inputs reach the brainstem regions responsible for the patterned motor actions of swallowing. It is by now established, that the sequential and rhythmic patterns of swallowing are formed and organized by a central pattern generator (CPG) located in the medulla oblongata. The CPG consists of two hemi-CPGs which, under physiological conditions, are tightly synchronized. The swallowing motor sequence is mainly generated in the ipsi-lateral hemi-CPG which transfers the premotor neuron signals to the contra-lateral CPG.[1] The CPG itself is organized into two groups of neurons: the dorsal swallowing group (DSG) in and around the nucleus of tractus solitarius (NTS) and the ventral swallowing group (VSG) just cranial to the ambiguus nucleus (NA). The DSG contains the generator neurons involved in the triggering, shaping and timing of the sequential or rhythmic swallowing pattern. The DSG activates all VSD premotor neurons which in turn distribute the swallowing

drive to the various motor neuron pools involved in swallowing. The multifunctional pattern generating circuits of the brainstem allow rapid modulation of orofacial behaviours (swallowing, respiration, chewing, coughing and vomiting).[2] Although our knowledge of the cortical regions involved in swallowing has grown substantially trough functional magnetic resonance imaging (fMRI) studies, the exact central control for swallowing is still not fully understood. The involvement of many functionally and spatially different cortical sites suggests multilevel control for the swallowing pathways. It has been proposed that the control system consists of parallel loops which are able to coordinate and integrate the complex sequentially based activation for swallowing.[3] The primary motor area, cingulated and insular cortices might all have essential roles in the coordination of the entire swallowing process.[4-6] Some investigators assume a functional dominance in swallowing[1,7] or a time-dependent shift of cortical activation from the left to right sensorimotor cortex during volitional swallowing.[8]

In summary, voluntarily and reflexive swallowing is controlled by widely distributed bilateral and multifocal cortical networks with apparently overlapping cortical regions. The primary sensory, motor, and cingulated cortices have a major role in these networks. The execution of the sensorimotor aspects related to swallowing rely on functionally connected pathways between (extra)pyramidal cortical motor planning regions, centres controlling the brainstem and cranial nerves as well as lower motor neurons.

Normal gastrointestinal tract (GI) function results from a balanced interaction between the enteric nervous system (ENS) and the central nervous system (CNS) which is called “the brain-gut axis”. The ENS neuronal as well as hormonal communications have important integrative functions. A detailed discussion of the hormonal pathways is beyond of the scope of this article. The ENS neural communications consist of the intrinsic afferent and motor neurons distributed along the mesenteric Auerbach and submucosal Meissner plexus, located in the walls of the gut. The afferent (vagal) sensory fibres terminate in the NTS of the hindbrain. The preganglionic motor innervations to the plexus arise from the dorsal motor nucleus of the vagus in the brainstem. The NTS and the vagal dorsal motor nucleus together comprise the dorsal vagal complex, important in the coordination of the muscular activity of the gut (vago-vagal reflex).[9] The oesophagus consists of a proximal striated muscle portion (upper oesophageal sphincter, UOS) and a distal smooth muscle portion (lower oesophageal

sphincter, LOS). At rest both sphincters are tonically contracted. Relaxation of the UOS (glossopharyngeal and vagal nerves) is initiated in the swallowing centre located in the medulla. Relaxation and contraction of the LOS (vagal and splanchic nerves) are initiated through local peristaltic activity of the oesophagus or distension of the gastric wall. Thus far the exact coupling of distinct interneurons in the NTS is not known. Also, it is not totally clear which cortical regions are mainly involved in processing information to the GI tract. It has been suggested that the anterior insular cortex (called "visceral cortex"), the prefrontal and sensory/motor regions, the cingulate gyrus, as well as the limbic regions, all participate in the integration of neuronal information to the GI tract.[10]

Pathophysiology of dysphagia in cerebral palsy

Dysphagia is a symptom that can be encountered in many different CNS disorders as well as those of the peripheral nervous system (PNS). We have chosen to use cerebral palsy (CP) as a model to describe the pathophysiology of dysphagia, as well as its diagnosis and therapeutic interventions.

CP is the most common physical disability in early childhood. It has been clinically defined as a group of motor, cognitive, and perceptive impairments secondary to a non-progressive defect or lesion of the developing brain. Epilepsy is a common problem in patients with CP. Seventy to 80% of CP cases arises from antenatal factors and birth asphyxia contributes approximately to 10% of the CP cases. Acquired cases after the prenatal period are usually related to central nervous system infection, trauma, strokes, and severe hypoxic events such as near-drowning. Genetic disorders and acquired insults follow a pattern of selective vulnerability during early brain development. The neonatal neuropathological correlates include specific and well known patterns of brain injury (see Table 1). We think that the understanding of dysphagia in the different CP subtypes might be facilitated by awareness of the topography of the neuronal injury.

A recent epidemiological study based on the analysis of children recorded by the Northern Ireland Cerebral Palsy Register (NICPR) between 1992 and 2009 showed a high incidence of dysphagia in any degree in children with CP.[11] Results from speech pathology testing and videofluoroscopic swallowing studies in CP children demonstrate the relationship between typically affected brain regions

Table 1 Regions with a predilection for hypoxic-ischemic neuronal injury

A.	Periventricular leucomalacie *(preterm babies and prolonged partial asphyxia)*
B.	Cortical and subcortical injury in a watershed parasagittal distribution *(term babies and prolonged milder hypoxic events).*
C.	Injury in the thalami, basal ganglia, hippocampi, dorsal mesencephalic structures, perirolandic cortex *(term babies and acute anoxic events).*
D.	Diffuse, destructive anoxic-ischemic event resulting in widespread replacement of cerebral cortex and white matter by one or more cavities of variable sizes (multicystic encephalopathy).

and the associated characteristic patterns of dysfunctional swallowing. Usually, clinical features such as delayed initiation and segmented swallowing during attempted volitional movement might be determined by cortical neuronal networks, while dysfunctional pharyngeal components of swallowing [i.e. automatic components of deglutition, such as throat clearing, laryngeal closure tasks] suggest subcortical brain injury and basal ganglia necrosis. In CP dysphagia is often characterized by problems in both the volitional oral movements and the more reflective pharyngeal phase of swallowing. Moreover, impaired ability to plan and coordinate swallowing with ventilation [e.g. greater propensity to swallow at abnormal times within the respiratory cycle, such as early inspiration after a thin liquid swallow and variable duration of the deglutition apnoea] are consistent with brainstem involvement.[12] A clinico-pathological correlation between differences in breath-swallow pattern and the risk for aspiration is likely. Clinically, aspiration manifests as frequently coughing, episodic aspiration, and occasional pneumonia. The overall incidence of pulmonary aspiration in CP due to oral motor dysfunctions is not yet known precisely, but this incidence must be high. Hospitalizations for respiratory reasons and presumed aspiration pneumonia in children with CP are common. It has previously been found in a study among 238 children with recurrent pneumonia that 48% had oropharyngeal incoordination with an aspiration syndrome, 50% of these children were diagnosed with CP [13]. Videofluoroscopic evaluation of dysphagia in CP has demonstrated pulmonary aspiration in 38%[14] to over 70% of the cases[15] and frequently the aspiration

occurred "silently" (without coughing).[14,16] Chronic pulmonary aspiration lead to chronic coughing, possibly sleep disordered breathing, impaired clearance of airway secretions and colonization by pathogenic bacteria of the airways, and there is a high-risk of ongoing lung parenchymal damage and death.[17]

In addition to aspiration due to dysphagia, chronic pulmonary aspiration in children with CP may also occur as a result of the gastro oesophageal reflux (GOR)[18]. The incidence of GOR has been estimated at approximately 50%[19] and might be explained by lesions in the swallowing centre located in the medulla oblongata leading to dysfunction of the vago-vagal reflex. In addition, GOR in children with CP may also result from direct lesions in cortical areas that modulate brainstem activity.[9,20]

Constipation, a common dysmotility disorder of the gut in children with CP, is often overlooked in this population. More than half of the children with severe generalized CP are constipated.[21] The high incidence of the dysmotility disorders emphasizes the defective integration and modulation of information within the brain-gut axis in CP, for which some investigators had proposed the term "Dysphagia-GOR complex", with a central role for the vagal nerve.[22] It is reasonable to assume that vagal disruption is responsible for defective feedback to the distinct cortical regions and brainstem which are associated with swallowing disorders, defective ventilation as well as dysmotility problems. At this time more studies are needed to investigate the clinical relevance of integrated breathing, GI and swallowing function on the health and nutritional outcomes of children with CP.

Drooling is caused by the swallowing disorder and occurs in 10% to 58% of children with CP.[23-25] From a clinical point of view it makes sense to distinguish between "anterior" and "posterior drooling". Anterior drooling is the unintentional loss of saliva from the mouth. Anterior drooling can impose a significant disability on children with CP, leading to psycho-social, physical and educational consequences. The most severely affected children may be rejected by their peers and even by their care-givers. Excessive anterior drooling destroys books, keyboards or computers, and as such threatens essential tools for education and communication in neurological disabled patients. In addition to cosmetic effects, drooling can produce peri-oral infections and can impair the dentition. In contrast to anterior drooling, so-called "posterior drooling" refers to the spill of saliva over the tongue through the faucial isthmus.[26] In particular the children with most severe pharyngeal dysphagia are at medical risk due to saliva aspiration to the

lungs. As mentioned above, aspiration in the child with CP often occurs without obvious coughing or choking (i.e. silently) and therefore chronic aspiration of saliva might not be diagnosed prior to development of significant lung injury.
In case of chemical irritation such as that caused by GOR, the salivary secretion is increased to protect the oral, pharyngeal, and oesophageal mucosa mediated by the vago-vagal complex in the brainstem. Unfortunately, in children with oral motor dysfunction this protective increased saliva volume may accumulate in the pharynx and/or oesophagus, leading to an increased risk for aspiration. It is still a matter of debate whether GOR can cause severe drooling and whether or not treatment of pathological GOR diminishes drooling in children with CP.

Practical implications

In short, dysphagia and drooling are frequently occurring symptoms and long-term neurological sequelae. The Dutch guideline for children with spastic cerebral palsy has included dysphagia and drooling as important issues. In our opinion at early stage particular note should be given to the important contribution that dysphagia and excessive drooling contribute to the burden of a child with CP and his/her family.
This is necessary because the younger brain is a highly dynamic structure with the capacity for profound structural and functional adaptation. We think that the formulation of rational prognostic statements and development of appropriate plans for management of dysphagia should be based on awareness of the topography of the brain injury (see table 2). This approach could also provide valuable information for the development of more effective intervention strategies for dysphagia in future.
At this moment, a systematic approach is recommended when clinicians meet patients who present with CP. The work-up needs to establish the medical and social consequences of the oral motor dysfunction and drooling. The oral motor dysfunction which is often characterized as “silent” aspiration requests an extended oromotor assessment and videofluoroscopic evaluation once. The combination of clinical features as coughing, fever and recurrent pneumonia should immediately raise the suspicion of chronic pulmonary aspiration, whereas the clinical combination of oral odour, hiccups and vomiting might suggest a GOR disease. Both clinical conditions need a pulmonary and a gastroenterological

Table 2 Relevance of the predilection regions for hypoxic-ischemic neuronal injury to swallowing

Site of lesion	Type of CP[a]	Mental Retardation	Swallowing		GOR
			Oral elements	Pharyngeal elements	
PVL	Spastic	+/-	+	+/-	+/-
(sub)Cortical	Spastic	+	+	+/-	+/-
Basal ganglia	Dyskinetic	+/-	+	++	+
Multicystic encephalopathy	Spastic > Dyskinetic	++	++	++	+

Abbreviations: CP = Cerebral Palsy; GOR = Gastro oesophageal reflux; PVL = Periventricular Leucomalacie; +/- = probably present; + = very likely present; ++ = evident
[a] = most encountered

diagnostic workup. The treatment of gut dysmotility and malnutrition can further help to improve the child's well-being. We recommend considering treatment for recurrent aspirations, GOR disease and drooling complaints at a very early stage, preferably with a multidisciplinary approach.

Summary Points

- The entire swallowing act is bilaterally controlled by a complex neuronal network in which the primary sensory/motor and cingulate cortices play major roles.
- The cortex is not only involved in the initiation of swallowing but also during pharyngeal and oesophageal swallowing.
- The sequential and rhythmic patterns of swallowing and related orofacial behaviours (i.e. respiration, coughing, vomiting) are formed and organized by multifunctional central pattern generators located in the brainstem.
- The execution of the sensorimotor aspects of swallowing rely on functionally connected pathways between (extra)pyramidal cortical motor planning regions, the brainstem controlling centre, cranial nerves and lower motor neurons.

- The wide range of swallowing, respiration, drooling and GI problems in CP and other neurological disorders can be understood in relation to (partial) disruption of these swallowing circuitries and the brain-gut axis which result in these disorders.
- Excessive oral secretions, under-nutrition, growth failure and the insidious evolution of lung disease are important causes of morbidity and mortality in children with CP. The multiplicity and potentially progressiveness of disabilities in CP highlight the need for a coordinated multidisciplinary program to manage bulbar symptoms, respiratory care and nutrition as early in the child's life as possible.
- Many of the concepts discussed here that are applicable to CP, will be also hold true for a wide variety of other neurological and developmental disorders.

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Chapter 3

Drooling in Cerebral Palsy: hypersalivation or dysfunctional oral motor control?

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Abstract

Objective: To investigate whether drooling in children with Cerebral Palsy (CP) in general and CP subtypes was due to hypersalivation.

Method: Saliva was collected from 61 healthy children (30 boys; mean age 9 years and 5 months and 31 girls; mean age 9 years and 6 months) and 100 drooling children (57 boys; mean age 9 years and 5 months and 43 girls; mean age 10 years and 1 month) with CP, of whom were 53 spastic, 42 dyskinetic, and 5 ataxic. Almost all children were affected bilaterally and 90 of them had GMFCS levels III or higher. The saliva was collected by means of the swab method. The intensity of drooling was evaluated using the Drooling Quotient.

Results: No differences were found in the flow rates, age, or gender between healthy children and drooling CP children. At additional sub-group analysis, the flow rates of dyskinetic subtype differed statistically from healthy school children.

Conclusion: This study supports the finding in previous studies that no hypersalivation exists in drooling CP children. Dysfunctional oral motor control seems to be responsible for saliva overflow from the mouth, whereas increased "unstimulated" salivary flow may occur in dyskinetic CP children due to hyperkinetic oral movements.

Introduction

Saliva is important in moistening the mouth and in the maintenance of oral hygiene. It lubricates the bolus while swallowing and helps in regulating oesophageal acidity.[1] Saliva is produced by three major paired glands – the parotid, submandibular, and sublingual glands – and by minor glands located throughout the oral and pharyngeal mucosa. The submandibular glands produce about 70% of high viscosity resting saliva. In addition, resting saliva is composed of secretions from the parotid (about 25%) and sublingual (about 5%) glands. The parotid glands are capable of producing great amounts of watery saliva while eating and drinking. The average person swallows approximately 600 ml of saliva per day, although in some individuals it might be as much as 1000 ml per day.

The pathway of saliva secretion is under autonomic control. Somatosensory, general, and special visceral (gustatory) afferents of the Vth, VIIth, IXth and Xth cranial nerves terminate in the Tractus Solitarius (NTS) and salivatory nuclei in the medulla oblongata. A controlling solitarial-hypothalamic circuitry has been proposed.[2,3] The parasympathetic stimuli enter the submandibular salivary glands by efferents of the VIIth and the parotid glands by efferents of the IXth. The preganglionic sympathetic fibers originate in the intermedio-lateral cell column of the 1st and 2nd thoracic cord segments and connect to postganglionic nerve fibers in the superior cervical sympathetic ganglion. These postganglionic sympathetic nerve fibers reach the salivary glands running along the external carotid artery. The secretion of saliva is regulated indirectly by the solitarial-hypothalamic circuitry ("smelling food makes one's mouth water") and by direct reflexes modulated by tactile, mechanical, and gustatory stimuli. The question remains whether cerebral palsy might include disruption of this regulatory mechanism as part of the encephalopathy.

Cerebral Palsy (CP) is the most common physical disability in early childhood. It has been clinically defined as a group of motor, cognitive, and perceptive impairments secondary to a defect or lesion of the developing brain.[4] Although drooling of saliva is usually considered abnormal in a child over four years of age, it has been estimated to occur in approximately 10% to 37% of children with cerebral palsy.[5,6] Primary functions such as lip closure, intraoral tongue suction, and swallowing may be disturbed due to neurodevelopment delay. In cases of saliva overflow, disturbed coordination of tongue mobility is the most likely cause,

since it is generally accepted that saliva production remains within normal limits. Hypersalivation or hypersialorrhea is rarely reported in children with cerebral palsy.[7-11] However, the causes of increased salivation are many: it can be an ictal finding in complex temporal lobe epilepsy; it can be caused by a variety of medications or irritating factors, such as teething, smoking, and gastroesophageal reflux; or it can be a symptom in an affective disorder. [12-15]

Previous studies were based on small numbers and used indirect methods (for example, cup-like devices or bib-weighing) to measure the whole saliva production, or measured stimulated (gauze-chewing or spitting) saliva flow rates in drooling CP children. But CP children in particular lack the strength to chew well and have trouble spitting. Therefore, it is possible that the assumption of normal saliva production is not correct because of methodological and power problems. The objective of this case-control study was to determine whether saliva production in drooling children diagnosed with cerebral palsy really is within the normal range. In the present study, the swab saliva collection method (swab test) was used, through which direct and exclusive salivary flow measurements were possible, taking dysfunctional oral motor control into account. In addition, we hypothesized that saliva secretion in children with dyskinetic CP is increased due to added mechanical stimulation of the salivary glands as a result of hyperkinetic oral movements.

Method

We collected data on 100 children (57 boys, age three to 19 years, mean age 9 years and 5 months (SD 3.9) and 43 girls, age four to 19 years, mean age 10 years and 1 month (SD 4.7)) diagnosed with CP and referred to the outpatient Multidisciplinary Drooling Centre of the Radboud University Medical Centre between 2001 and 2007 because of moderate to profuse drooling. The children were categorized by CP type, the ability to speak, having convulsions, and the severity of motor disturbances assessed by the Gross Motor Function Classification Scale (GMFCS).[4] The GMFCS was proven to be a valid and reliable tool which remains relatively stable over time.[16,17] The children were enrolled using the inclusion and exclusion criteria in Table 1. Written informed consent was obtained from all parents. The research was conducted in accordance with the national and

Table 1 Inclusion and exclusion criteria

Inclusion criteria
Children (male and female, age 3-19 years).
Confirmed diagnosis of cerebral palsy (medical history and neurological examination, MRI, EEG).
Score of three or higher on the Drooling Severity and Frequency Scale, indicating moderate to profuse drooling.
Informed consent (parents/caregiver).
Exclusion criteria
Enrolment in another medical study.
Previous surgical procedure for saliva control.
Use of drugs that interfere with saliva secretion (anticholinergic and neuroleptic drugs, benzodiazepines).

international ethical standards and the Hospital's Human Research committee approved the study.

The control group consisted of 61 healthy children recruited from primary schools, ranging in age from eight to 12 years: 30 boys (mean age 9 years and 5 months; SD 0.9) and 31 girls (mean age 9 years and 6 months; SD 1.2). None of the children reported having any complaints suggestive of salivary gland dysfunction or needed any medication that would influence the salivary secretion. The parents of all children gave written informed consent. The data for the control group were collected at the start of the study in 2001 and the results were published earlier.[18] Saliva was collected under standardized conditions using the method described by Rotteveel et al in 2004.[18] After the mouth was dried with sterile gauze, three absorbent cotton rolls (Salivette®, Sarstedt BV, Etten-Leur, The Netherlands) were placed in the mouth for five minutes: one roll under the tongue at the orifices of the ducts of the sublingual and submandibular glands and two rolls in the upper vestibules at the openings of each parotid duct. In the present study, we labeled all flow in the floor of the mouth as submandibular flow. The cotton-rolls were weighed before and after the procedure using an electronic scale, which

was sensitive to 0.01 g. The increase in weight during the five minutes interval was then converted into ml saliva/min. The drooling intensity was evaluated by the Drooling Quotient (DQ), a direct semi-quantitative observational method. [19,20] Every 15 seconds (40 observations in 10 minutes) the presence of newly formed saliva on the lips was assessed. The DQ is expressed as a percentage estimated from the ratio of observed drooling episodes and the total number of observations. Both the swab testing and the DQ method were performed in healthy school children and drooling children with CP in the morning at least one hour after the last meal, while they were watching television. Measurements were performed by two experienced speech language therapists.

Statistical analysis

The submandibular and parotid flow rates were compared between the healthy school children and the children with CP using non-parametric statistics (Mann-Whitney U and Kruskal-Wallis tests), because of non-normal distributions for these parameters, especially in the CP children. All participants were categorized by gender and age. Because of the wider age range in CP children, the CP group was split up in three age groups (three through seven years, eight through 12 years, and 13 through 19 years of age). In addition, the total CP group was subdivided into spastic and dyskinetic CP subtypes. The magnitude of the associations between the DQ and the total salivary flow for all CP children and for the CP subtypes was assessed using the Spearman rank correlation coefficient. All analyses were performed with SPSS 14.0 for Windows. Results with two-tailed p-values <0.05 were consisted statistically significant.

Results

Almost all children diagnosed with CP (53 spastic, 42 dyskinetic, and 5 ataxic subtypes) were affected bilaterally and 90 children had a score of III or higher on the Gross Motor Function Classification Scale (GMFCS). Epileptic seizures were in control in 46 children and only four children suffered from intractable seizures. Fifty children had never had any convulsions at all. Only one child had normal

articulation, whereas 37 children had dysarthric speech and 62 were anarthric (Table 2). All children with CP had a score of three or higher on a drooling severity and frequency scale, indicating moderate to profuse drooling.[21] Each child had some kind of oral motor dysfunction such as tongue protrusion, malocclusion, reduced intra-oral sensitivity, or reduced ability to voluntarily control the movements of lips, tongue, and jaw.

Table 2 Patients characteristics

Number	Total	100
CP subtype	Spastic Dyskinetic Ataxic	53 42 5
Affected side	Unilateral Bilateral	2 98
Convulsions	None Controlled Intractable	50 46 4
Medications	All anti-epileptic drugs were allowed, except benzodiazepines	
Speech	Unimpaired Dysarthric Anarthric	1 37 62
GMFCS	I II III IV V	3 7 24 34 32

Legend to table 2: CP = Cerebral Palsy; GMFCS = Gross Motor Functional Classification Scale (I = performing gross motor skills including running and jumping but reduced speed, balance, and coordination, II = limitations walking on uneven surfaces and inclines, and walking in crowds or confined spaces, III= walking indoors or outdoors on a level surface with an assistive mobility device, wheelchair as needed, IV = reliance on wheelchair,
V = no means of independent mobility)

All children could perform the swab testing and no one had to be withdrawn from our study. In healthy school children the median submandibular flow rate was 0.32 ml/min (range 0.10-0.56), whereas the median parotid flow was 0.11 ml/min (range 0.02-0.44). The median submandibular flow rate in children with CP was 0.34 ml/min (range 0.08-1.09) and the median parotid flow 0.14 ml/min (range 0.00-0.60) (see Table 3). Neither the submandibular flow rates (p = 0.331) nor the parotid flow rates (p = 0.373) were statistically significantly different between the healthy school children and the CP children.

Table 3 Results

	Controls	CP	Spastic CP	Dyskinetic CP
N	61	100	53	42
Subm (ml/min)	0.32	0.34	0.34	0.38
p-value		*0.331*	*0.873*	*0.047**
Par (ml/min)	0.11	0.14	0.10	0.18
p-value		*0.373*	*0.583*	*0.040**
DQ (%)	0.0	23.2	20.0	31.9
p-value				*0.015**

Legend to table 3: N = Number; Subm = Submandibular flow (ml/min); Par = Parotid flow (ml/min); DQ = Drooling Quotient (%); CP= Cerebral Palsy; * statistically significant different.

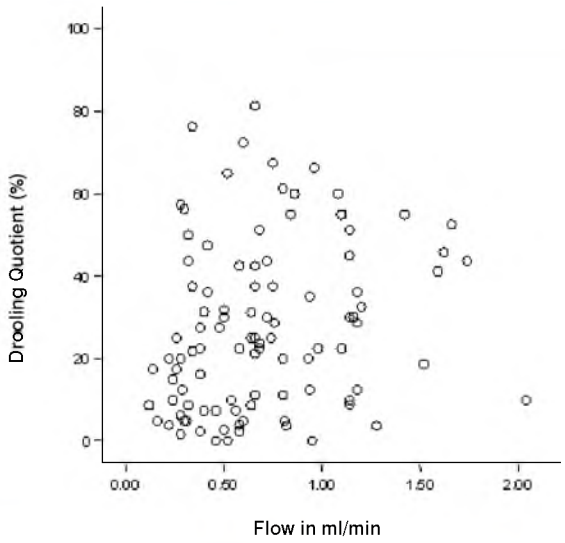
The mean ages of the school children (9 years and 6 months; SD 1.0) and the CP children (9 years and 8 months; SD 4.2) were not different (p = 0.846), but the age range of the CP group was much wider than that of the healthy school children. However, there were no differences in the submandibular flow rates between the three age groups of drooling CP children (p = 0.749). The median parotid flow rates differed somewhat between the three age groups (p = 0.017), pointing towards lower flow rates among children in the oldest age group. No differences existed in gender between the controls and the CP children (p =

0.336), nor in the median salivary flow rates between control girls and girls with CP (submandibular $p = 0.801$, parotid $p = 0.622$) and between controls boys and boys with CP (submandibular $p = 0.195$, parotid $p = 0.099$).

No differences were found in gender ($p = 0.288$) and mean age ($p = 0.428$) between the spastic and dyskinetic CP subtypes. The median submandibular and the parotid flow rates in the spastic subtype were 0.34 ml/min (range 0.08-0.68) and 0.10 ml/min (range 0.00-0.60). In the dyskinetic subtype, the median submandibular and parotid flow rates were 0.38 ml/min (range 0.08-1.09) and 0.18 ml/min (range 0.02-0.48), respectively. The parotid flow rate was statistically significantly different between the spastic and dyskinetic subtypes ($p = 0.029$), whereas the difference between the submandibular flow rates ($p = 0.069$) almost reached statistical significance. No differences were found in the salivary flows between the controls and the spastic CP children. However, the salivary flows were statistically significantly different between the healthy school children and the children with dyskinetic CP (submandibular $p = 0.047$, parotid $p = 0.040$) (see Table 3)

The median DQ in the drooling children with CP was 23.2 % (range 0.0-81.0 %). The difference in the DQ between the spastic subtype (20.0 %; range 1.8-81.3 %) and the dyskinetic subtype (31.9 %; range 0.0-76.3 %) was statistically significant ($p = 0.015$). A mild correlation (spearman's rho = 0.28; $p = 0.004$) existed between the total salivary flow in the drooling CP children and the DQ (Figure 1). The correlation between the total flow and the DQ in spastic CP children was also mild (spearman's rho = 0.38; $p = 0.005$), but there was no correlation between the total flow and the DQ in the dyskinetic CP subtype (spearman's rho = 0.07; $p = 0.683$).

Figure 1 The magnitude and direction of the association between the total salivary flow and the Drooling Quotient in all children with CP (Spearman's rho = 0.28)



Discussion

The present study did not show substantial differences in the salivary submandibular and parotid flow rates between healthy school children and drooling CP children in general, nor between age and gender. However, the results did show differences in the flow rates between healthy school children and the dyskinetic CP subtype. Drooling in children with dyskinetic CP is more intense in comparison to children with spastic CP, but does not seem to be correlated with the total salivary flow.

To our knowledge, the present case-control study on drooling is the largest study published so far, with as many as 161 participants measured with the swab saliva collection method allowing us to calculate the saliva secretion per salivary gland. With these numbers, we were able to detect differences of half the standard deviation for both the submandibular and the parotid flows with a power of 80%.

It remains difficult however, to study a heterogeneous population, such as children with cerebral palsy. Although, this heterogeneity gave us the opportunity to look at subtypes of CP, it may be an important limitation of the study, as it may have masked other differences. On the other hand, all cases were well defined and the control group and patient groups matched in gender and mean age. However, the age range in the CP group was much wider than in the control group, no age-related decline or increase in the distribution of the salivary submandibular flows was noted in the children from three up to 19 years of age, but the parotid flows seemed somewhat unstable over the age groups. Despite numerous studies on salivary flow rates, the effect of ageing on salivary secretion remains obscure due to conflicting observations. One study found that the unstimulated parotid flow rate increased significantly with increasing age in children ranging from three to 16 years[22], whereas other studies suggested that high salivary activity in school children decreased with increasing age[23] or reported no age-related decline or increase of unstimulated salivary flow in eight to 12-years-olds.[18] Apparently, age is not an important factor when measuring salivary flow rates up to adolescence.

In other studies on drooling CP children, the total amount of stimulated saliva was collected by cup-like devices or by a gauze-chewing procedure or bib-weighing technique.[11,22] These studies demonstrated the influence of disturbed oral motor control on drooling in children with CP. Senner suggested that drooling CP children swallow less frequently.[22] Sochaniwskj et al demonstrated a diminished ability to control the oral phase of swallowing and problems in the coordination of the sequence of muscle activation in swallowing. All CP children, both those who drool and those who do not, had a diminished subconscious swallowing frequency.[9] Lespargot suggested that an initial oral suction stage is abnormal in all drooling CP children, which might be a factor that leads to pooling in the oral cavity.[8] Tahmassebi and Cruzon found some kind of disturbed oral motor control most often characterized by incomplete lip-closure, tongue protrusion, stiff and slow tongue movement, lack of voluntary control of jaw and tongue, and oral dyskinesia.[11] This might be consistent with a disturbance in the swallow circuits as mentioned in the introduction. So, when studying drooling in CP children, it seems advisable to consider the influence of dysfunctional oral motor control. Using the absorbent swab testing method, any urge to swallow can be left out of consideration due to the position of the cotton-rolls adjacent to the orifices of the

ducts of the salivary glands, preventing any leakage of saliva in the oral cavity. The swab method has proven to be a highly reproducible method and it has been reported that the cotton-rolls method in handicapped children is a useful tool to evaluate the unstimulated salivary flow rate of both the submandibular and parotid glands.[18,24] Unlike previous studies, we were able to measure the unstimulated salivary flow directly and exclusively, independent of any kind of swallowing dysfunction. However, any hyperkinetic oral motor activity could not be ruled out or prevented.

Despite the fact that we did not find arguments for hypersalivation in the total CP group, clinically the drooling children with dyskinetic CP appear to be a subgroup. Due to mechanical stimulation of the salivary glands in these children, the total daily saliva secretion (about 600 ml in general) was increased by an amount of approximately 200 ml per day or even more. The contribution in added saliva secretion of the parotid glands was twice as large as that of the submandibular glands. This can be a relevant phenomenon in the management of drooling. In other words, treatment of drooling in spastic CP children should mainly be focused on the saliva flow of the submandibular/lingual glands, while in dyskinetic CP the target seems to be both the submandibular/lingual and parotid flows.

Conclusion

This study supports the finding in previous studies that no hypersalivation exists in drooling CP children in general. However, there are arguments for increased salivary flow in drooling dyskinetic CP children due to hyperkinetic oral motor activity. In contrast to previous studies, this has been supported by direct measurements of resting "unstimulated" salivation in a large population using a method that decreased potential influences of oral motor control disturbances.

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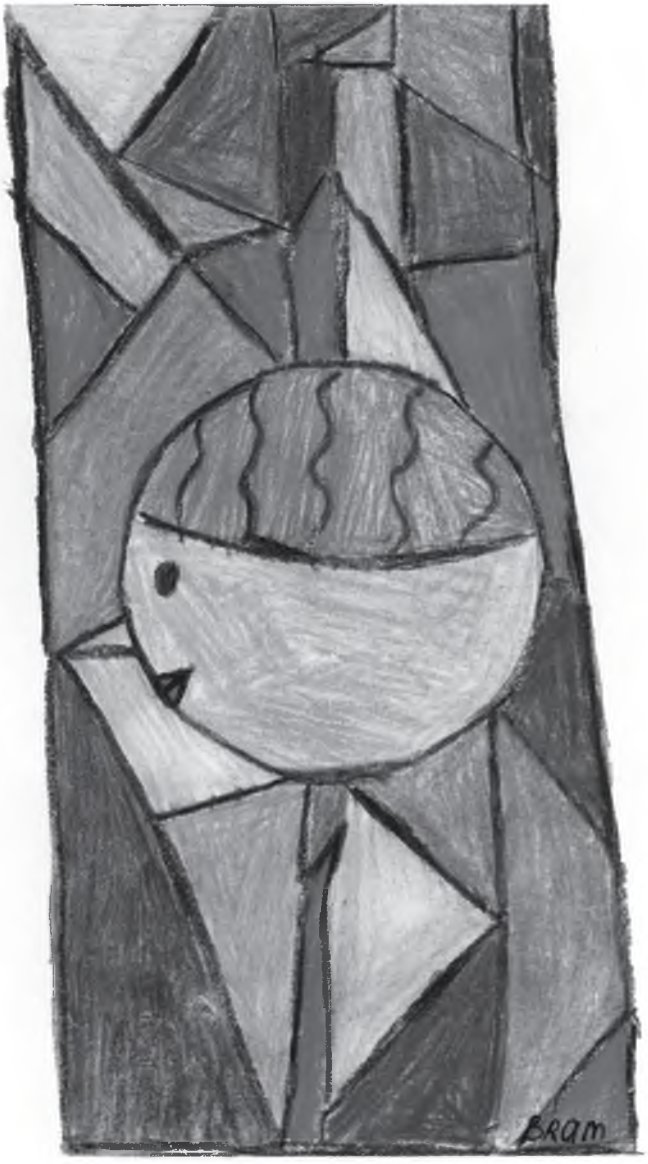
Part II



4

Chapter

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

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Abstract

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 Outcome Measures 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 2 months and 19 after 8 months ($P < .001$). The mean VAS score decreased from 80 at baseline to 53 after 2 months and increased to 66 after 8 months ($P < .001$). 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.

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]

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] score, 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

Table 1 Inclusion and exclusion criteria

Inclusion criteria
Non-progressive congenital neurological disease. Invalidating drooling (TDS ≥ 3). Treated with Botulinum Toxin to the submandibular glands at least once.
Exclusion criteria
Known hypersensitivity to Botulinum Toxin or any part of the formulation. Missing baseline measurement, or missing >1 follow-up measurement. Known use of other agents that influence drooling during the treatment. Progressive disease.

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* .05 was considered statistically significant.

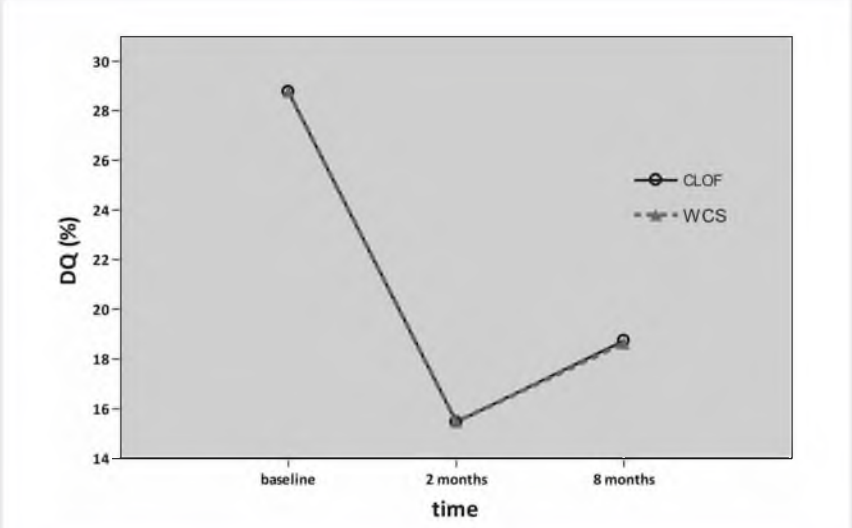
Results

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 8 months 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

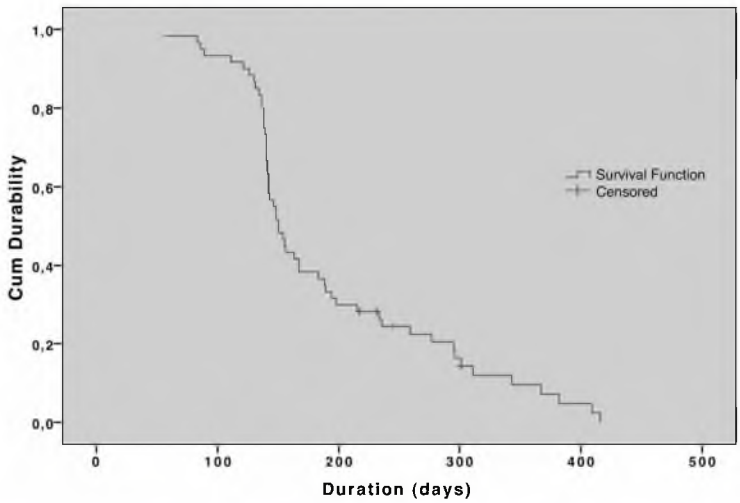
Figure 1 From a mean baseline value of 28.7, the DQ showed a statistically significant mean reduction to 15.5 after 2 months and 18.7 after 8 months ($P < 0.001$)



CLOF, for last observation carried forward;
WCS, worst-case scenario.

(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 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 8 months 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.

Figure 2 Kaplan-Meier analysis of longevity of Botulinum Toxin injection for patients who showed a response to Botulinum Toxin after 8 weeks (n=61)

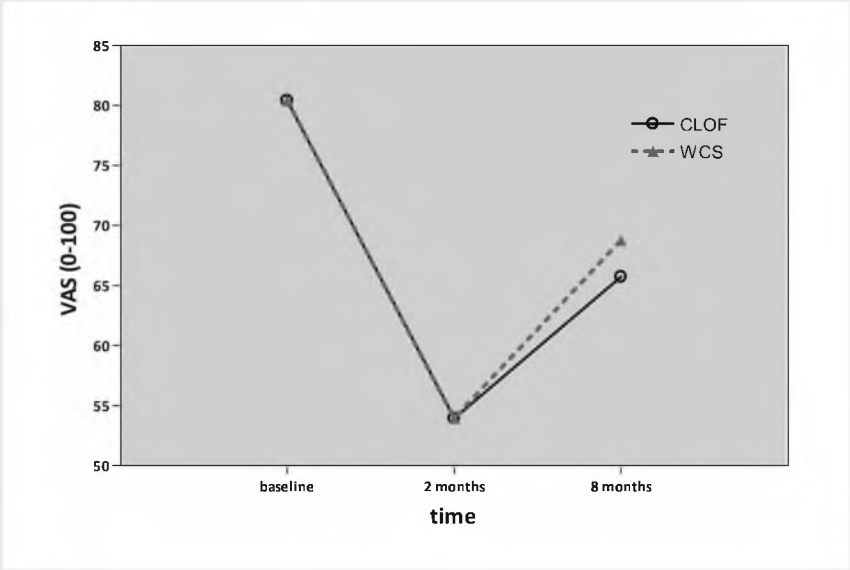


Duration of effect shown in days. Median: 150, IQR: 138-235.

Secondary outcomes

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 2 months, the mean VAS score had fallen from a baseline value of 80.4 to 53.9 ($P < .001$). After 8 months, the VAS score had risen to 65.7 ($P < .001$) (Table 2). Although there were more missing VAS score values (6 after 2 months, 20 after 8 months) than DQs, no meaningful differences were found between the CLOF and WCS analyses; only the 8-month 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 2 months and 26.0% after 8 months.

Figure 3 From a mean baseline value of 81.2, the VAS fell to 53.3 two months after injection ($P < 0.001$). After 8 months, the value of 69.7 was still significantly lower than at baseline ($P < 0.001$)



CLOF, for last observation carried forward; WCS, worst-case scenario.

Table 2 Mean differences between baseline and follow-up measurements

Pairs of observation	DQ – difference (95%-CI)		VAS – difference (95%-CI)	
	CLOF	WCS	CLOF	WCS
BI-2 months	-13.2 (-16.2 – -10.1)	-13.2 (-16.2 – -10.1)	-23.5 (-29.3 – -17.5)	-23.6 (-29.6 – -17.5)
BI-8 months	-9.9 (-12.9 – 6.9)	-10.0 (-13.0 – -7.1)	-12.1 (-17.3 – -7.0)	-15.3 (-21.1 – -9.7)
2 months-8 months	3.2 (0.8 – 5.7)	3.2 (0.7 – 5.7)	12.2 (7.1 – 17.3)	15.4 (9.7 – 21.1)

BI indicates baseline; CLOF, carry observation forward; WCS, worst-case scenario.
Based on paired-samples *t*-tests, 2-sided $P \leq 0.05$.

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 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 2 months (1.7%), which had resolved after 8 months.

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 8 months.

Comment

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; 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.[14] 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 therefore 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 anti-cholinergic 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 nonprogressive 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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5

Chapter

Does motor performance matter in Botulinum Toxin efficacy for drooling?

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Abstract

The aim of this study is to define factors that influence therapy outcome of submandibular Botulinum Toxin injections for drooling in children with cerebral palsy and / or mental disability.
It is postulated that differences in response may be explained by the variation of dysfunctions in the various cerebral palsy subtypes.
Prospectively collected data were evaluated of 80 spastic and 48 dyskinetic children, of whom 70% had an IQ < 70. In addition the data of 23 fully ambulant children with exclusively mental disability were examined.
Flow and Drooling Quotient were assessed at baseline and at 8 weeks after injection. Following treatment both the Drooling Quotient and submandibular flow decreased in all children. Morbidity associated with the procedure was limited. Ninety three children responded to Botulinum. Decrease of submandibular flow in these children was associated with reduction of parotid flow. In the non-responders, spread across all three diagnostic classifications, parotid flow increased after injection. Response failure is characterized by increased parotid flow after injection, however the precise role of parotid flow in therapy failure remains unclear. We cannot predict who will respond to Botulinum Toxin to treat drooling.

Introduction

Drooling is normal in the growing child up to the age of 18 months. Beyond the age of four years it is abnormal and frequently persists in children with poor neuromuscular coordination, mental disabilities, as well as in children who lost the structural integrity of their jaws, lips or oral cavity.[1] It is widely accepted that drooling in Cerebral Palsy (CP) is caused by oral motor dysfunction.[2-5] An exception to this may be for those with dyskinetic disorders where the abnormal oral movements may constantly stimulate the parotid glands to produce more saliva.[2] Moreover, the risk of oromotor disorders and excessive drooling increases in wheelchair-bound persons and in children with any degree of intellectual impairment.[6] The inadequate swallowing of saliva may increase the risk of aspiration as well as contributing to impaired communication due to the constant presence of saliva.

In several prospective, controlled clinical trials significant reduction of saliva with a maximum response at 2 to 8 weeks was found after Botulinum Toxin type A injection.[7] Botulinum Toxin inhibits the acetylcholine release at the autonomic terminals of the salivary glands decreasing the secretion of water. However, after 10 years experience in our multidisciplinary drooling clinic it was observed that up to 30 percent of the children the drooling severity and frequency did not change significantly after submandibular Botulinum Toxin A injection. In our previous study we suggested that increased saliva production due to constant stimulation of the parotid glands due to hyperkinetic oral movements might account for drooling in those with dyskinetic disorders. In addition, peripheral sympathetic inhibition of salivary reflex secretion has been described as being related to non-physiological conditions, for instance after Botulinum Toxin application.[8] To evaluate these possibilities the present cohort study explored the effect of submandibular Botulinum Toxin type A at the parotid salivary flow in three distinct clinical groups of children: children with spastic CP, dyskinetic CP and mental disability without CP. We hypothesized that treatment efficacy will be similar across all three groups with similar rates of responsiveness.

In view of the anticholinergic property of Botulinum Toxin, it is likely that the watery component of saliva will be reduced and that after receipt of Botulinum Toxin, the salivary viscoelasticity increases.[9] Interesting, it has been reported that saliva viscosity reduces after Botulinum Toxin injections.[10] The opposite phenomenon

(much thinner salivary aspect post Botulinum Toxin) may indicate that the reflex salivary secretion from other salivary glands increases after submandibular Botulinum Toxin type A. As such, we subhypothized that non-responsiveness to submandibular Botulinum type A may be caused by compensatory parotid flow.

Materials and Methods

Data from 126 individuals (age 3-21 years, mean age 10 years (y) and 11 month (mo) (SD 4y and 11mo); 81 males and 45 females) who were screened at the outpatient drooling clinic of the Radboud University Nijmegen Medical Center, The Netherlands and had undergone treatment with an injection of Botulinum Toxin type A into the submandibular glands between February 2000 and October 2008 were analyzed. Children were categorized as having CP or mental disability based upon Developmental Age[11] and the severity of motor disturbances as assessed by the Gross Motor Function Classification System (GMFCS).[12,13] The children with CP were subdivided by the predominant motor type.[14] All of the 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).[15] None had undergone previous treatment with Botulinum Toxin type A or surgery for saliva control.

For the statistical analyses, the following classifications were used: the first to investigate the influence of three categories (spastic CP subtype, dyskinetic CP subtype, and mental disability not classified within the CP group), and secondly to explore the differences within the CP group (the two CP subtypes). All medications taken to treat drooling or to influence salivary secretion (especially benzodiazepines and neuroleptic drugs) were stopped at least three months before the start of the treatment. No limits were set concerning the use of antiepileptic drugs and the child's level of cognitive development. Data from children diagnosed with ataxic CP subtype, Worster Drought Syndrome or a progressive neurological condition were excluded from the study. 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 children.

An ultrasound-guided injection of Botulinum Toxin type A was injected bilaterally into the submandibular salivary glands divided over two sites per gland using a 25 G needle (Spinocan®). A total dose of 50U Botox® (Allergan B.V., Nieuwegein, The Netherlands), diluted with 1.5 ml saline, was used. Drooling intensity and salivary flow were measured at baseline and at 8 weeks after injection. Drooling intensity was evaluated using the Drooling Quotient, a semi quantitative observational method (expressed as a percentage) representing the actual clinical appearance of saliva loss. The Drooling Quotient 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. The presence or absence of drooling was assessed every 15 seconds (40 observations in 10 minutes).[16]

To measure the salivary flow rate we used the "swab method": after the oral cavity had been dried with sterile gauze three absorbent dental cotton rolls (Salivette®; Sarstedt B.V., Etten-Leur, The Netherlands) were placed in the mouth for periods of 5 minutes: one roll under the tongue directly in front of the orifices of the submandibular and sublingual glands, and two rolls in the upper vestibules at the openings of the parotid ducts.[17] Two well-trained speech and language therapists conducted all the assessments which always took place in the morning, 1 hour after the last meal. The cotton rolls were weighed before and after the procedure using an electronic scale, which is sensitive to 0.01g. The roll under the tongue and the two upper vestibules-rolls were weighted separately to be defined as submandibular and parotid flow. The increase in weight during the 5-minute period was converted into milliliters of saliva per minute to determine salivary flow rate.

At each assessment the medical history was taken, especially regarding feeding, speech, coughing and salivary aspects.[18] In addition, the parents were asked to register all possible side effects in a diary.

Data analysis

Baseline evaluation. 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 three categories using non-parametric statistics (Kruskal-Wallis and Mann-Whitney-U Tests), because of

non-normal distribution of these measures. Missing data were seldom, but on occasion adjusted by the overall mean of the group.

Therapy response. Multivariable analyses of variance (MANOVA) with a repeated measures structure were used to identify differences in mean submandibular and parotid flow, and Drooling Quotient across time using the baseline and 8 weeks assessment as variables. In addition, when either of the analyses had a significant effect, a post hoc test was performed to determine the differences between the groups. Since we wanted to control for the Type I error rate, Bonferroni adjustment for multiple comparison was used.

Therapy failure and clinical variables. A successful therapy response was defined as 30 percent submandibular flow reduction and/or 50 percent reduction of the Drooling Quotient. The 30% demand has been previously reported and is explained by the estimated measurement error of the swab method to evaluate the salivary flow rate.[17] A 50% reduction in the Drooling Quotient reflected a clinical relevant change.[7] The submandibular glands produce about 60 to 70% of baseline salivary flow. In the event the Drooling Quotient is reduced by 50% after Botulinum Toxin injections, the change of flow from the submandibular glands, being the only gland exposed to this intervention, must have added substantially to this reduction. All participants were categorized as responsive or as unresponsive to submandibular Botulinum Toxin type 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. In addition, for each group (responsive or unresponsive to Botulinum Toxin type A) we computed the Spearman's correlation coefficient to define the magnitude of the associations between spastic or dyskinetic CP subtype, mental disability, mobility level and treatment response. For all statistics, the level of significance for two-tailed p-values was set at ≤ 0.05. All statistical procedures were carried out using SSPS 17.0 for Windows.

Results

All children completed the treatment. See Table 1 for clinical characteristics. There was no significant difference in the baseline demographic variables between the groups, with the exception of mobility. The mobility level differed between the children with mental disability and the total CP group ($U=196.00; p<0.001$) and also between the children with spastic and dyskinetic CP subtype ($U=1038.00; p=0.02$). Because of limitations related to the clinical diagnoses, it was not always possible to obtain simultaneous scores for the swab tests and the Drooling Quotient at one measurement session. The swab testing at baseline could be performed in 109 children and in 100 children at the 8 week assessment. At baseline the Drooling Quotient was determined in 120 children and at 8 weeks in 109 children. Missing data (14%) occurred at different assessment moments randomly spread over all children. Data of the median

Table 1 Clinical characteristics

All patients (n=126)	**Spastic CP 62/126 (49%)**	**Dyskinetic CP 45/126 (36%)**	**Mental disability without CP 19/126 (15%)**
Affected side	Quadriplegic 58 Hemiplegic 4	Bilateral affected	Not applicable
Mean Age (SD)	11y 4mo (4y 5mo)	10y 2mo (5y)	11y (6y 4mo)
Sex (male/female)	43/19	27/18	11/8
DA			
<4y	34 (55%)	22 (49%)	15 (79%)
4-6y;IQ<70	11 (18%)	9 (20%)	0 (0%)
4-6y;IQ>70	2 (3%)	1 (2%)	0 (0%)
>6y	15 (24%)	13 (29%)	4 (21%)
GMFCS*			
I	0 (0%)	0 (0%)	All ambulatory
II	6 (10%)	2 (4%)	
III	21 (34%)	6 (13%)	
IV	18 (29%)	19 (42%)	
V	17 (27%)	18 (40%)	

CP = Cerebral Palsy; SD = Standard Deviation
DA = Developmental age
GMFCS = Gross Motor Functional Classification System
*Kruskal-Wallis Test: significantly difference between the three groups

submandibular and parotid flow rates, and Drooling Quotient at baseline and at 8 weeks after injection of all participants are shown in Table 2. For the results between the diagnosis categories at baseline and after submandibular Botulinum Toxin type A therapy see Table 3.

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

Drooling parameters	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)	**32.5** (0.0-97.5)	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)

CP = Cerebral Palsy
Sm0, Par0 and DQ0 = median submandibular and parotid flow and Drooling Quotient at baseline
Sm8, Par8, DQ8 = median submandibular and parotid flow and Drooling Quotient at the 8 weeks assessment
bold Mann Whitney U test = significant difference for median Drooling Quotient at baseline between children with spastic and with dyskinetic CP; $p=0.03$

Table 3 Results between the diagnosis categories

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

CP = Cerebral Palsy; Vs. = versus; DQ = Drooling Quotient; Sm = Submandibular flow
Par = Parotid flow
* Post hoc Test = non-significant
† Test of Between-Subjects effects = non-significant

Therapy failure and clinical variables

According to our definition, 93 children were full responders and 33 children were unresponsive to Botulinum Toxin type A (see Table 4). At baseline there were neither statistically significant differences between the median submandibular flow rate (U=1189.50;p=0.06) nor the median Drooling Quotient (U=1302.50; p=0.20), whereas the difference for the median parotid flow rate was statistically significant (U=1099.00;p=0.02) between the children responsive or unresponsive to Botulinum Toxin type A. Furthermore, in the children responsive to Botulinum Toxin type A, decrease of submandibular flow rate across time was accompanied with decrease of parotid flow, whereas in children unresponsive to Botulinum Toxin type A the parotid flow rate increased marginally. The difference in the parotid flow

Table 4 Characteristics of the children whom are responsive or unresponsive to Botulinum Toxin type A

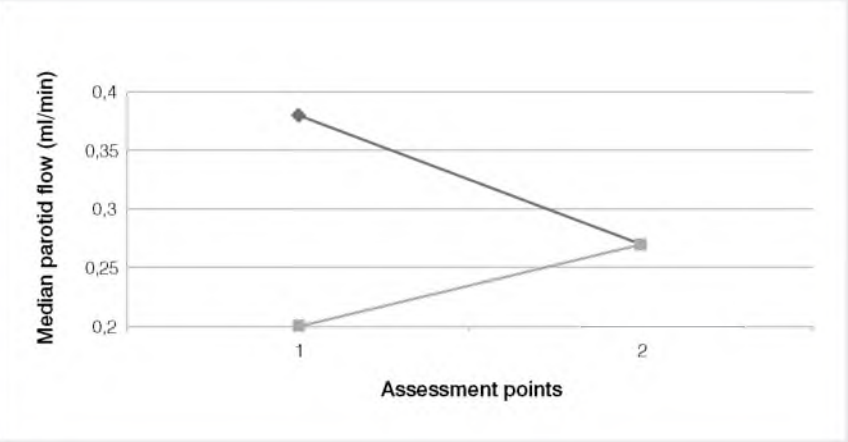
All patients (n=126)	Responders (n=93)	Non-responders (n=33)
Spastic CP* Dyskinetic CP Mental disability without CP	44/62 (71%) 35/45 (78%) 14/19 (74%)	18/62 (29%) 10/45 (22%) 5/19 (26%)
Mean age (SD)	11y 1mo (5y 6 mo)	10y 4mo (4y 8mo)
Sex (male/female)	61/32	20/13
DA<4y* 4-6y;IQ<70 4-6y;IQ>70 >6y	52 (56%) 18 (19%) 2 (2%) 21 (23%)	19 (58%) 2 (6%) 1 (3%) 11 (33%)
Sm0 ml/min (range) Par0 ml/min† DQ0 % Sm8 ml/min (range) Par8 ml/min DQ8 %	0.42 (0.06-1.09) 0.38 (0.04-1.25) 28.1 (0.0-97.5) 0.18 (0.02-0.54) 0.27 (0.0-0.86) 12.5 (0.0-57.5)	0.34 (0.08-0.60) 0.20 (0.0-1.06) 22.5 (0.0-80.0) 0.28 (0.12-0.85) 0.27 (0.04-1.12) 17.5 (2.5-65.0)

SD = Standard Deviation, y= year , mo=month, DA = developmental age
Sm0, Par0 and DQ0 = median submandibular and parotid flow and Drooling Quotient at baseline
Sm8, Par8 and DQ8 = median submandibular and parotid flow and Drooling Quotient at the 8 weeks assessment point
* Spearman's correlation coefficients = non-signifiant
† p=0.02

rates over time was statistically significant ($F(1;124) = 20.92;p<0.001$) between the responders and non responders. The median parotid flow rates across time between children responsive and unresponsive to Botulinum Toxin type A are presented in Figure 1. Clinical variables as Developmental Age (r_S=-0.03;p=0.71), mobility level (r_S=0.08;p=0.38) and spastic or dyskinetic CP (r_S=0.08;p=0.43) did not significantly correlate with response percentage.

Although injections were usually well tolerated, there were several minor side effects in this series (see Table 5).

Figure 1 Median parotid flow rate in time between children responsive and unresponsive to Botulinum Toxin type A



= responsive to BoNT-A (n=97)
= unresponsive to BoNT-A (n=33)
X-axis = assessment points; 1 = at baseline, 2 = at 8 weeks after injection
Y-axis = median parotid flow rate (ml/min)

Table 5 Side-effects after Botulinum Toxin type A at the 8 weeks assessment

	Spastic CP (n=62)		Dyskinetic CP (n=45)		Mental disability without CP (n=19)	
	R	NR	R	NR	R	NR
Increased salivary viscosity Reduced salivary viscosity	9/62 *(15%)* 1/62 *(2%)*	2/62 *(3%)* 0/62 *(0%)*	16/45 *(36%)* 1/45 *(2%)*	3/45 *(6%)* 0/45 *(0%)*	1/19 *(5%)* 0/19 *(0%)*	0/19 *(0%)* 0/19 *(0%)*
Problemful swallowing	2/62 *(3%)*	2/62 *(3%)*	2/45 *(4%)*	0/45 *(0%)*	0/19 *(0%)*	2/19 *(11%)*
Raised 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 odour	0/62 *(0%)*	0/62 (0%)	0/45 *(0%)*	0/45 *(0%)*	1/19 *(5%)*	0/19 *(0%)*

CP = Cerebral Palsy
R = responder to Botulinum Toxin type A
NR = non-responder to Botulinum Toxin type A
number of patients with side effects / total number of patients

Discussion

This prospective study suggests that submandibular Botulinum Toxin type A treatment for drooling has similar effects across severely affected children with spastic or dyskinetic CP, or those with mental disability without CP. The data did not support the phenomenon of increased salivary flow due to mechanical stimulation of salivary glands in dyskinetic CP, however the findings did suggest that drooling is clinically distinct between children with spastic and dyskinetic CP. Although increased salivary parotid flow rates in children unresponsive to submandibular Botulinum Toxin type A were found, the role of parotid flow in therapy failure could not be settled in the current study. Therapy failure might mainly be explained by factors that influence the intra oral management of saliva such as head position, lip closure and disturbed oral movements instead of biological factors such as neurological regulatory mechanisms of salivary flow.

As generally discussed in CP literature, the rate of mental disability and dyskinesia increases as functionality decreases. Against this background, we concluded that our group represented not an average group of children with CP, but a very severely affected group.[19,20]

The overall percentage of responders (74%) was in accordance with a former study (70%).[7,21] Criticizers could argue that an overestimation of the effect due to the used imputation method is possible. Nevertheless, the mean imputation method provided unbiased estimates in current study, because the missing values met the strong assumption of being missing completely ad random.[22]

Earlier it was suggested that in those children with dyskinetic disorders drooling might be caused by increased production of saliva due to constantly stimulation of the parotid glands. In the present study we were unable to demonstrate this. A possible explanation for this could be that the swab method technique itself plays a role. The position of the cottons rolls limited movements of the jaw and tongue considerably ("fixed mouth"), hindering potential salivary gland stimulation in children with dyskinetic CP during the assessments. The increased drooling intensity in dyskinetic CP assessed by the Drooling Quotient observation, where voluntary oral motor function was still possible ("dynamic mouth"), suggested that mechanical stimulation of the salivary glands might contribute to drooling in the dyskinetic CP subtype. Furthermore, the children with dyskinetic CP seemed to have better residual swallowing functions

explained by the clear decrease of the Drooling Quotient after submandibular Botulinum application.

The clinical response failure was approximately 26% in our study. Since ultrasound was used, incorrect application of Botulinum Toxin type A would not be likely as a reason for the observed therapy failure. Besides, adequate doses were used and response failure due to antibody formation to the first Botulinum Toxin type A application can be considered to be irrelevant. Moreover, it was very unlikely that chemical diffusion of the Toxin via local vasculature or by gravity influence caused the parotid flow to decrease as none of the participants had complaints of bulbar muscle weakness.[23]

One possible explanation for the observed therapy failure might be the 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 in particular the parasympathetic nerve supply, has been interrupted secretion from almost all salivary glands will entirely cease.[24] It is understood that under normal conditions inhibition of reflex salivary secretion is centrally controlled. However, under non-physiological conditions, for instance after Botulinum Toxin application, peripheral sympathetic inhibition of salivary secretion comes into action.[8] It might be possible that the concept of insufficient peripheral sympathetic inhibition of the salivary secretion did play a role in unresponsiveness to Botulinum Toxin. Another explanation for response failure may be the contribution of factors related to handling of saliva. An earlier study showed that the response rate cannot be improved by simply injecting the submandibular and parotid glands concurrently.[25] Moreover, in the present study it was observed that the response to submandibular Botulinum Toxin type A changes according to the definition of good clinical response. As the definition of response was defined as a 30 percent submandibular flow reduction ("biological factor"), the size of the effect decreased from 76% to 65% and even to 47% if response was defined as a 50 percent reduction of Drooling Quotient (linked to the ability to control saliva). Therefore, it might well be that "factors related to handling of saliva" even more than "biological factors" contribute to therapy failure.

Until now we are unable to predict who will respond to Botulinum Toxin type A. Moreover, univariate parameters such as motor impairment ("quality of movement"), mobility level and mental ability ("functional ability"), or even baseline Drooling Quotient and flow rates had no decisive value to discriminate

between successful or unsuccessful therapy response in this study. Remarkably, before injection an important difference in the parotid flow rates was found between the children responsive and unresponsive to Botulinum Toxin type A (see Figure 1), however we were not able to explain the pathophysiology of the difference.

A disadvantage of present study might be the omission to measure the cares' perception as ultimate test of treatment effectiveness.[26,27] However, we specially wanted to focus on factors that might affect the saliva-control-intervention rather to evaluate the overall effectiveness of the intervention.

In conclusion, there were arguments for increased salivary flow due to hyperkinetic oral movements in dyskinetic CP and probably the children with dyskinetic CP might have better residual swallowing functions. However, the efficacy of submandibular Botulinum Toxin type A to treat drooling in children with CP subtypes or with mental disability without CP appeared to be similar. Future research is needed to provide tools to predict who will be a responder and to settle the contribution of parotid flow in response failure.

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Chapter 6

What could predict effectiveness of Botulinum Toxin to treat drooling: *A search for evidence of discriminatory factors on the level of body functions or structures*

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Abstract

Background: The treatment of drooling is important to families that experience the daily impact and research to elucidate clinical factors that play a role in the outcome of drooling treatment should be encouraged.

Aim: To define clinical factors that influence therapy outcome of submandibular Botulinum Toxin (BoNT-A) injections for drooling.

Methods: Prospectively collected data of 128 children with cerebral palsy were evaluated; 80 spastic and 48 dyskinetic movement disorder, mostly Gross Motor Function Classification System III and higher; over 70% had an IQ < 70. In addition, 23 fully ambulant children with exclusively intellectual disability were treated for drooling by ultrasound-guided injections of BoNT-A into the submandibular glands. Salivary flow rates and drooling quotients were measured at baseline and at 8 weeks after injection. Extensive information about the oral motor performance was gathered. Successful clinical response was defined as a 50 % reduction of the baseline Drooling Quotient; 85 children were responsive to BoNT-A and 66 children unresponsive.

Results: Five nominated clinical factors that possibly could influence saliva reduction (head position, lip seal, voluntary control over the tongue, control of voluntary movement functions, and mental age) did not influence the responsiveness to BoNT-A.

Interpretation: Other variables need to be considered to predict the outcome of BoNT-A treatment. This article describes the first attempt to reveal the contribution of body functions and structures to the outcome of BoNT-A submandibular injections.

Introduction

Earlier drooling treatment results showed that up to 30 % of patients did not respond to submandibular injection of Botulinum Toxin Type A (BoNT-A) if response was defined as a 30% reduction of submandibular salivary flow in combination with a 50% reduction of the Drooling Quotient (DQ).[1,2] Given the number of non-responders, further research necessitates to search for factors that cause therapy failure.

BoNT-A injections result in a substantial direct effect on submandibular flow (SF) and have an indirect effect on the saliva regulatory mechanisms. Hence, the therapy effect of submandibular BoNT-A injections might be influenced on the one hand by pharmacological properties (type of Botulinum Toxin, dilution, injected dosage, secondary antibody response, and pharmacokinetics in relation to brand) and on the other hand by clinical variables (e.g. gross motor functions, cerebral palsy (CP) subtype, oral motor functions, mental ability). The primary purpose of the present cohort study was to reveal body functions and structures (as defined by the International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY)) that could influence therapy outcome.

The majority of individuals with CP produce normal amounts of saliva, and it is generally accepted that the amount of saliva is not the decisive factor responsible for drooling in children with CP.[3] In the absence of evidence, researchers thus far have suggested a positive contribution to drooling severity of poor head control, dysfunctional oralmotor control, a decreased swallow frequency, reduced intra-oral suction, dysarthria severity, and a degree of malocclusion in children with CP.[4-8] No correlation has been found between mobility level and the amount of saliva drooled.[5] Yet, little is known about clinical factors in relation to treatment outcome of submandibular gland BoNT-A application to treat drooling. Controlled data are not available, and it is unclear why some children with CP or developmental delay who drool respond well to BoNT-A while others only respond to a lesser extent. To date only a few population studies focusing on behavior modification therapy for drooling reduction have included clinical factors. It has been shown that saliva control and consequently drooling severity is most positively associated with age and the ability to swallow, control the head, and walk without aid.[9] Currently, there is no agreement about what child characteristics will distinguish between a "successful" or "unsuccessful" therapy response after submandibular BoNT-A injections.

This article describes the first attempt to reveal the contribution of body functions and structures to the outcome of BoNT-A submandibular injections to treat drooling. Body function and structure items, assumed as relevant clinical factors that might contribute to the treatment outcome are listed in Table 1. Given the costs of BoNT-A and the fact that anesthesia is needed, it is important to know what factors might influence treatment outcome of BoNT-A injections and to formulate strict indications for this therapy.

Table 1 Definition of the Clinical Factors

Variables	Definition
Head Position	Ante flexion vs. lateral flexion-retro flexion-normal
Tongue protrusion	Permanently-often vs. sometimes-never
Lip seal in daily activity	Impossible-clearly different vs. slightly divergent-normal
Voluntary tongue control	No–almost never vs. sometimes–normal
Developmental Age	< 4 years and 4-6 years with IQ < 70 vs. 4-6 years with IQ > 70 and > 6 years
Control of voluntary movement functions	GMFCS I-III (ambulatory) vs. IV-V (non-ambulatory)
TOM-Dysarthria	Very serious-serious vs. moderate-mild-no dysarthria
DSS-Dysphagia	Very serious-serious vs. moderate-mild-minimal-no dysphagia

vs. = versus.
GMFCS = Gross Motor Classification Function System: I = performing gross motor skills including running and jumping but reduced speed, balance, and coordination, V = no means of independent mobility
TOM = Therapy Outcome Measure (Dutch and modified version of the subscales for dysarthria)
DSS = Dysphagia Disorder Survey (Dutch version)

Method

Participants. Prospectively collected data from 151 children (mean age 10 years 10 months, SD 4 years 10 months) screened in the outpatient drooling clinic at the Radboud University Nijmegen Medical Centre, The Netherlands between February 2000 and March 2010 were evaluated. The children were categorized as having CP or intellectual disability based upon Developmental Age (DA).[10] The children with CP were classified according to the predominant motor type.[11] The severity of motor disturbances was assessed by the Gross Motor Function Classification System (GMFCS).[12] Most of the children with CP had a mobility score of III or higher on the GMFCS; more than 70% had an Intelligence Quotient (IQ) below 70. All children with intellectual disabilities were ambulant, and had an IQ below 70.

Inclusion criteria were 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).[9] None of the participants had undergone previous BoNT-A therapy or surgical procedures for saliva control. All medications to control drooling or influencing salivary secretion were stopped at least 3 months before the start of the study. This research was conducted in accordance with national and international ethical standards. The Regional Committee on Research Involving Human Subjects approved the study. Informed consent was obtained from the parents or caregivers of all children.

Exclusion. No limits were set with regard to the child's level of cognitive development. Children with an ataxic CP subtype, or the Worster-Drought Syndrome as well as children with a progressive neurological condition were excluded from the study.

Procedures. A single ultrasound-guided injection of BoNT-A was given bilaterally into the submandibular salivary glands. A total dose of 50U Botox® (Allergan B.V., Nieuwegein, The Netherlands) was used. During a rest situation when a person does not eat or drink the submandibular glands produces approximately 60 – 70% of the whole amount of saliva. The activity of the parotid glands, being anatomically the largest glands, increases during gustatory stimulation, a function with which we did not want to interfere.

Scoring. All children were evaluated after the first injection for the drooling quotient, the salivary flow as well as for clinical factors. Those were assessed at baseline and 8 weeks after injection.

After completing a thorough literature study, we identified that the following factors are suggested to contribute to drooling severity: head position, lip seal, voluntary control of tongue movements, control of voluntary movement functions, and mental age (see Table 1). The described factors all are authors opinions and in this sense reflect 'best practice' being a low level of evidence. Nevertheless, it is postulated that these factors could explain the lack of response to BoNT-A drooling treatment because clinical arguments support this approach.

The drooling quotient (DQ). a semi quantitative observational method (expressed as a percentage), was scored according to the original design by recording all episodes of drooling during 10 minutes. A drooling episode was defined as new saliva being present on the lip margin or dripping from the chin. The presence or absence of drooling was assessed every 15 seconds (40 observations in 10 minutes).[13] We postulate that the DQ more obvious represented clinical aspects, and in view of clinical relevance the DQ was used as the indicator of clinical effects. In general, the submandibular glands produce about 60 to 70% of baseline salivary flow. In the event the DQ is reduced by 50% after BoNT-A, the change of flow from the submandibular glands, being the only gland exposed to this intervention, must have added substantially to this reduction. Thus, a 50% reduction in the DQ reflected a clinical relevant change.[1,14] Therefore a successful clinical response was defined as a 50% reduction of the DQ at the 8 weeks assessment in this study.

To measure the salivary flow rate, after drying the oral cavity with sterile gauze, three absorbent dental cotton rolls (Salivette®; Sarstedt B.V., Etten-Leur, The Netherlands) were placed in the oral cavity for a 5 minute-period: below the tongue in front of the orifices of the submandibular and sublingual glands as well as in the upper vestibules at the openings of the parotid ducts.

The morning and the 1-hour after the meal assessments were performed by a specially trained speech and language therapist (SLT). In addition, the SLT also gathered extensive information about the oral motor performance. The cotton rolls were weighed before and after the procedure using an electronic scale, which was sensitive to 0.01 g. The increase in weight over the 5-minute period was converted into milliliters of saliva per minute to determine salivary flow rate.

The decrease of the salivary submandibular flow (SF) was only used to monitor the drooling control intervention.

The parotid flow (PF) profiles, for each of the three categories, spastic CP,

dyskinetic CP and intellectual disability, were evaluated to indentify compensatory raised parotid flow after submandibular gland BoNT-A injections.
Dysarthria severity was scored using the Dutch and modified version of the subscales for dysarthria of the Therapy Outcome Measure (TOM).[15] The Dutch version of the Dysphagia Disorder Survey (DDS) was used to assess the overall feeding and swallowing functions.[16]

Statistical analysis

Data analysis included the following descriptive statistics: the median salivary flow rates and median DQ. To identify differences in the median submandibular and parotid flows over time Wilcoxon Signed Rank Tests were used. The clinical factors related to therapy response were evaluated using chi-square statistics, and logistic regression analyses were used to predict therapeutic response. The Nagelkerke R^2-statistic was used as an indicator of the variation explained by the model.
The missing data for the flow rates and DQs were adjusted by geometric mean substitution; the missing values of the clinical factors were substituted by hot-deck imputation (substitution with data from another observation of the same subject). For all statistics, the level of significance for one-tailed p-values was set at ≤ 0.05. An exception was made for the chi-square testing; the level of the one-tailed p-values was set at < 0.2 or a significant difference was assumed if the relationship to therapy outcome could be considered as biologically plausible. All statistical procedures were carried out using SSPS 17.0 for Windows.

Results

All children completed the treatment. See Table 2 for clinical characteristics. The swab testing at baseline could be performed for 129/151 children and, for 131/151 children at the 8-week assessment. At baseline the DQ was determined for 147/151 children and at 8 weeks for 148/151 children. All missing data points for the flow rates and DQ occurred at different assessment points, in different children. The geometric mean for the variable was imputed for missing data.

Table 2 Clinical Characteristics

	Responders N=85 (56%)		**Non-responders N=66 (44%)**	
Mean age *(SD)*	10y 8mo *(4y 10mo)*		10y 11mo *(4y 11mo)*	
Sex M/F	52/33		38/28	
Diagnosis • Spastic CP • Dyskinetic CP • Intellectual disability	 40/80 (50%) 34/48 (71%) 11/23 (48%)		 40/80 (50%) 14/48 (29%) 12/23 (52%)	
Drooling Characteristics	**Pre**	**Post**	**Pre**	**Post**
• Median SF *(range)*	0.40 *(0.0-2.10)*	0.18 *(0.02-0.54)*	0.41 *(0.08-0.98)*	0.24 *(0.04-0.85)*
• Median PF *(range)*	0.34 *(0.04-4.10)*	0.27 *(0.0-1.02)*	0.33 *(0.0-1.19)*	0.33 *(0.0-1.18)*
• Median DQ *(range)*	32.5 *(0.0-100.0)*	2.5 *(0.0-40.0)*	24.7 *(0.0-80.0)*	25.0 *(2.5-68.0)*

(*SD*) = Standard Deviation; Y = year, Mo = month; CP = Cerebral Palsy; SF = Submandibular Flow in ml/min; PF =Parotid Flow in ml/min; DQ = Drooling Quotient in %; Pre = Before Botulinum Toxin injection; Post = After Botulinum Toxin injection

According the definition of response, 56% of the children showed a good clinical response to submandibular BoNT-A as measured by the DQ (Table 2). This also means that a substantial proportion of the study populations did not meet the criterion of adequate clinical improvement, being a 50% reduction of the DQ. All children showed a statistically significant reduction in the SF whether their clinical drooling was responsive or unresponsive to submandibular BoNT-A injections ($z = -7.60$, $p < 0.001$ resp. $z = -5.24$, $p < 0.001$)).

Surprisingly, children with dyskinetic CP that showed a positive response to the treatment also showed a statistically significant decrease in PF ($z = -2.49$, $p = 0.01$). This was not true for children with spastic CP type or exclusively mentally disabled children showing a positive response to drooling treatment. They had no statistically significant difference between the pre treatment and post treatment medians for the PF ($z = -0.82$, $p = 0.41$ resp. $z = -0.82$, $p = 0.42$).

For the non-responders per diagnosis category there was no statistically significant reduction in PF over time (spastic CP ($z = -0.46$, $p = 0.65$); intellectual disability ($z = -1.18$, $p = 0.24$); dyskinetic CP ($z = -0.46$, $p = 0.65$)).

Although not found to be statistically significant in the univariate analysis, five factors (see table 3) are considered to be biologically plausible variables related to treatment outcome; they were analyzed by logistic regression. Note that the results from the logistic regression have been presented only to provide an indication of how much of the variability in the treatment could possibly be explained by a model containing just these five clinical variables. In addition, missing data per variable are given (Table 3).

Table 3 Factors contributing to therapy response

Variables	Missing data[a]	Univariate analysis (p-value)
Head position	19/151	***0.17***
Lip seal in daily activity	2/151	***0.28***
Voluntary tongue control	26/151	***0.32***
DA	0/151	***0.28***
Control of voluntary movement functions	0/151	***0.29***
TOM-Dysarthria	5/151	0.47
DSS-Dysphagia	2/151	0.42
Tongue protrusion	8/151	0.42
Head position, Lip seal, Voluntary tongue control, DA and Movement functions if combined		**Logistic regression** R^2 =0.27; p=0.18

The clinical factors showed no relation to therapy response in the univariate analysis as well as in logistic regression analyses. The Nagelkerke R^2 should be between 0 and 1, with 0 denoting that model does not explain any variation and 1 denoting that it perfectly explains the observed variation.
DA = Developmental Age
TOM = Therapy Outcome Measure (the Dutch and modified version of the subscales for dysarthria)
DSS = Dutch version of the Dysphagia Disorder Survey
[a] all randomly missing values adjusted by Hot-deck Imputation
Bold (italic) = biological plausible factors

Discussion

The purpose of this investigation was to determine factors, as derived from the ICF-CY body function and structure paragraph, relevant to treatment outcome of submandibular gland BoNT-A injections in children with CP or intellectual disability. The results from this cohort study demonstrated that the BoNT-A submandibular injections resulted in a statistically significant reduction in the saliva production from the submandibular glands. This significance of the submandibular flow reduction was not expressed in the primary treatment outcome as investigated by the drooling quotient (DQ). The SF was reduced regardless the fact whether the child was classified as a responder of a non-responder.

In the current study we choose the DQ as measure, because it reflects more obvious the clinical outcome and relevance of the drooling treatment. According to the chosen strict response definition, 56% of the children showed a positive clinical response to submandibular BoNT-A application as measured by the DQ. In previous studies the success rate was higher because a broader definition of response was taken.[1,2] However, the response rate of about 50% is in accordance with a recent study of our group.[17]

As generally discussed in the literature, the predominant motor types for individuals with CP are spasticity (91%) and dyskinesia (4%).[18] Our study group does not reflect an average population of CP since the selection of patients was mainly based on the severity of drooling introducing a specific kind of selection. Dyskinetic CP was represented with 32% and most of them had a GMFCS level of III and higher. As functionality decreases the percentage of children with dyskinetic CP will increase up to 75%.[19] Against this background, we concluded that the raised percentage of dyskinetic CP from average 4% up to 32%, presented more functionally affected individuals in our study.

On the level of body function this study repeatedly confirmed that BoNT-A has a positive outcome on salivary flow reduction. In spite of careful investigation and statistical analysis, no evidence could be found that the five nominated clinical factors (head position, lip seal, voluntary control over the tongue, control of voluntary movement functions, and mental age) would influence the clinical outcome to BoNT-A as measured by the DQ. Given the large number of patients in our cohort and the adequate methodological and statistical approach, this is

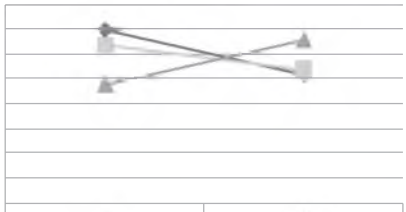
an important finding. When grouped together these factors cannot indicate or predict which of the children will be responders or non-responders with the chosen level of response. This is the first step to reveal the apparently complicated issue of body functions and structures playing a role in drooling and its treatment outcome. These observations imply that other variables need to be considered to predict the outcome of BoNT-A treatment.

The five investigated clinical factors seem logical to influence treatment outcome. For example head position and lip seal are influenced by gravity. The same reasoning also applies to movement functions which are clearly related to head position. Previous investigations demonstrated that tongue mobility strongly is correlated with drooling and drooling control.[6] Therefore, it seems plausible that the ability to control the tongue is an important factor related to therapy outcome, following the factor quantity of saliva reduction. Although to date no correlation has been found between mental age and successful training for drooling control[13], the risk of oromotor impairment is raised by any degree of intellectual impairment[20] and the relationship between mental age and therapy outcome might be expected. To what extent this might be of importance for occupational therapy setting, remains open for debate and cannot be answered by the present study design.

While the cluster of clinical variables could not predict which children would be responders, the converse is also true. Children with one or more 'negatively rated' clinical factors still can have a positive clinical outcome. In view of the fact that not all injections are successful, it should be kept in mind that the local effectivity of BoNT-A is not the same as the effectiveness on the functional level. The discrepancy between observed local effect (ie decrease of flow) and the clinically reported "functional efficacy" (i.e. insufficient drooling control) remains to be proven.[21] Therefore, we evaluated the relationship between reflex saliva secretion of the parotid gland and observed therapy outcome. After BoNT-A, the reflex salivary secretion from all glands will be peripheral sympathetic inhibited[22] and the median PF was expected to fall. Indeed, in some children the median PF decreased whether they were responder or not. However, it is more interesting to note that some children were even able to increase the parotid saliva secretion (Figure 1). There is evidence that the Hypothalamic-Pituitary Axis activity is altered in children with neurological disabilities.[23-25] We suggest that peripheral sympathetic inhibition causes a decrease of the salivary secretion of the parotid gland after BoNT-A in almost all children[26], but it might well be that dysfunctional

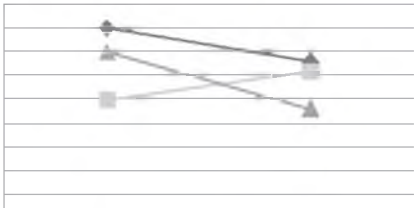
Figure 1 Median Parotid Flow (PF) in responders and non-responders

Median PF in responders



	1	2
Spastic CP	0,35	0,26
Dyskinetic CP	0,32	0,27
Mental disorder	0,24	0,33

Median PF in non-responders



	1	2
Spastic CP	0,40	0,33
Dyskinetic CP	0,25	0,31
Mental disorder	0,35	0,23

X-axis = assessments; 1 = assessment at baseline, 2 = 8 weeks-assessment
Y-axis = median parotid flow in ml/min
CP = Cerebral Palsy

regulation by hypothalamic pathways explains why in some children the reduced submandibular salivary flow remains uncompensated by sufficient increase of PF. Thus the biological local effect (decreased submandibular flow) is answered (immediately) by an adaptive (peripheral) reaction. Moreover, we hypothesized that therapy outcome to submandibular BoNT-A could also be influenced by

compensatory strategies of the central circuitries responsible for saliva production. Presumably, such concepts about BoNT-A as discussed here in the light of drooling, may be applicable for other applications of BoNT-A.

The findings of this study should be considered in light of the following limitations. First, this study took place in a rather heterogeneous population. Secondly, a disadvantage of present study might be the omission to measure the perception of carers.[27]

In sum, the response to submandibular BoNT-A on the combination of the clinical variables, and treatment results were not influenced by head position, lip seal, voluntary control of tongue movements, control of voluntary movement functions, and mental age. Research to elucidate clinical factors that play a role in the outcome of drooling treatment should be encouraged. Prediction of treatment outcome is important because Botulinum Toxin administration is costly and has to be repeatedly applied, while needing anesthesia.

Future research is also needed to evaluate the neuropharmacological properties of BoNT-A and other drooling treatment regimes in relation to therapy outcome (e.g. additionally injection of the parotid gland, repeated BoNT-A applications, dose-finding studies). However, it has been reported that improvement of the response rate will not be achieved by dose adjustments, which is likely to induce more adverse effects.[28] Different treatment strategies, such as combination of BoNT-A injections into the submandibular as well into the parotid glands had only slightly improved response rate.[29]

Finally, the potential influence of an altered Hypothalamic-Pituitary Axis activity in children with neurological disabilities and drooling should be investigated.

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7

Chapter

Thickened saliva after effective management of drooling with Botulinum Toxin A.

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Abstract

Aim: To evaluate the rheological properties of saliva after submandibular BoNT-A injections.

Method: We enrolled fifteen children diagnosed with spastic (9) or dyskinetic (6) quadriplegic CP; GMFCS IV or V (age three to 17 years, 11 males and six females) and two children with intellectual disability (IQ<70) who experienced moderate to severe drooling. Salivary flow rate using cotton rolls and Drooling Quotient were measured at baseline and at different intervals after BoNT injections up to 24 weeks. The mucin concentration was analysed before and after BoNT treatment.

Results: The submandibular flow rate (baseline 0.38 ml/min; 24 weeks after injection 0.26 ml/min) as well as the Drooling Quotient (baseline 42.5%; 24 weeks 28.80%) were substantially reduced with a concomitant increase in mucin concentration within eight weeks after BoNT application (from 0.612 to 1.830 mg/ml). Parents observed thickened saliva in nine children. Swallowing and chewing were problematic in seven children. Two of these children needed treatment with mucolytics because of pooling of thickened saliva in the throat.

Interpretation: In making decisions about the use of BoNT-A, the risk of problems with masticatory and swallowing functions due to thickening of saliva after BoNT treatment should be taken into account.

Introduction

Local injection of Botulinum Toxin (BoNT) into the salivary glands is used for treatment of drooling. BoNT causes a temporary inhibition of SNAP-25: the presynaptic acetylcholine-exocytotic synaptosomal-associated protein with a molecular weight of 25 kDa. As a result, the gland's secretory (water) capacity is depressed. After BoNT injection, the basal saliva secretion is usually sufficient to moisten the oral cavity and to facilitate swallowing of food. Incidental side-effects have been reported, such as flu-like symptoms lasting for less than two days, swallowing difficulties, viscous saliva and dryness of the mouth, transient slight weakness of the masseter muscle or mouth openers, and rarely jaw dislocation [1-6].
Human saliva serves multiple functions in the oral cavity, including moistening of food, facilitation of mastication and swallowing, and cleaning and lubrication of the oral mucosa [7]. The seromucous sublingual, submandibular, and palatine glands secrete mucins which coat and protect the epithelial tissue of the oral cavity, and give the typical viscoelastic character to saliva. Salivary mucins are primarily wetting agents which play a role in lubricating the tissue-environmental interface to produce low friction [8,9].
We observed that the saliva became sticky in some children after intraglandular botulinum application and assumed that sticky saliva may cause swallowing problems due to increased protein concentrations and changed salivary viscosity causing more friction [10]. Previous studies focused on the effect of BoNT on salivary proteins such as secretory immunoglobulin A (immune system) and amylase (digestion), but salivary mucins, responsible for the rheological properties of saliva, have not been studied before [11,12].
In view of the anticholinergic properties of BoNT, it is likely that the watery component of saliva will be reduced and that the concentration of mucins will increase post-BoNT injection. The present study was undertaken to investigate the viscoelasticity of saliva after BoNT application and to evaluate the consequences of changed viscoelasticity. Increased friction due to less effective wetting properties of saliva after BoNT application may cause intraoral discomfort and less effective mastication and swallowing.

Method

Seventeen children (age three to 17 years, 11 males and six females) who were screened in the outpatient drooling clinic at the Radboud University Nijmegen Medical Centre, The Netherlands between 2000 and 2001 were enrolled in this study. Fifteen children were diagnosed with spastic (9) or dyskinetic (6) CP. They were bilaterally affected and were wheelchair bound with a Gross Motor Function Classification Scale IV or V. They had no oral speech and demonstrated moderate to severe dysfunctional oral motor control. Two children (one 12-year-old boy and one seven-year-old girl) with intellectual disability (developmental age < four years) were also included. These two children were ambulant without aids, but were unable to speak. All 17 children were fed orally and had a score of three 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) [13]. None had previous surgical procedures for saliva control. All medications taken to treat drooling or influencing salivary secretion were stopped at least three months before start of the study. No limits were set with regard to the child's level of mental development. The research was conducted in accordance with the national and international ethical standards and the Regional Committee on Research Involving Human Subjects approved the study. Written informed consent was obtained from the parents or caregivers of all children.

An ultra-sound-guided injection with Botulinum Toxin A was given bilaterally into the submandibular glands. A total dose of 30 U up to 50 U of Botox® (Allergan B.V., Nieuwegein, The Netherlands) was used. The drooling intensity and the salivary flow were measured at baseline and at two, four, eight, 16 and 24 weeks after injection. A least two mucin activity measurements within eight weeks after treatment with BoNT-A were required for inclusion in this study. At each assessment point, comprehensive details were collected about the child's drooling, feeding, speech, presence or absence of coughing, and characteristics of saliva[14]. In addition, the parents were asked to register all possible side effects in a diary. Cervical auscultation was performed to look for pooling of secretions in the throat. The drooling intensity was evaluated with the Drooling Quotient (DQ), a semi-quantitative observational method (expressed as a percentage). The DQ was scored according to its original design during two periods of 10 minutes separated by a 60-minute break. An episode of drooling was defined as

new saliva present on the lip margin or drooling from the chin. Every 15 seconds (40 observations in 10 minutes) the presence or absence of drooling was assessed [15] To measure the salivary flow rate, absorbent dental cotton rolls (Salivette®; Sarstedt B.V., Etten-Leur, The Netherlands) were placed directly in front of the orifices of the submandibular and sublingular glands for five-minute intervals after drying the oral cavity with a sterile gauze. The assessments were conducted by the same speech language therapist, always in the morning, and one hour after the last meal [16]. The cotton rolls were weighed before and after the procedure using an electronic scale, which was sensitive to 0.01 g. The increase in weight during the five-minute interval was converted into ml saliva/min.
After weighing, the cotton rolls were centrifuged and the saliva samples were stored at -20°. The total mucin concentration (U/ml) in thawed saliva was analysed using ELISA with mAb F_2 as described previously [17]. Briefly, isolated mucins were 2-fold serially diluted in 0.1 M $NaHCO^3$ (pH 9.6) starting from 2 ug/ml and incubated overnight at 4°C in polystyrene wells of microtiter plates. After rinsing, mAb F_2 (approximately 1 ug/ml) was added and the samples were incubated for one hour at 37°C. Bound antibodies were probed with peroxidase conjugated to rabbit anti-mouse immunoglobulin (Dakopatts, A/S, Glostrup, Denmark), using o-phenylene-diamine (0.4 mg/ml) and H^2O^2 (0.012 %) as substrates. Color development was measured at 490 ran with a Dynatech MR7000 microtiter plate reader (Dynatech Laboratories Ltd., Billinghurst, UK).

Statistical Analysis

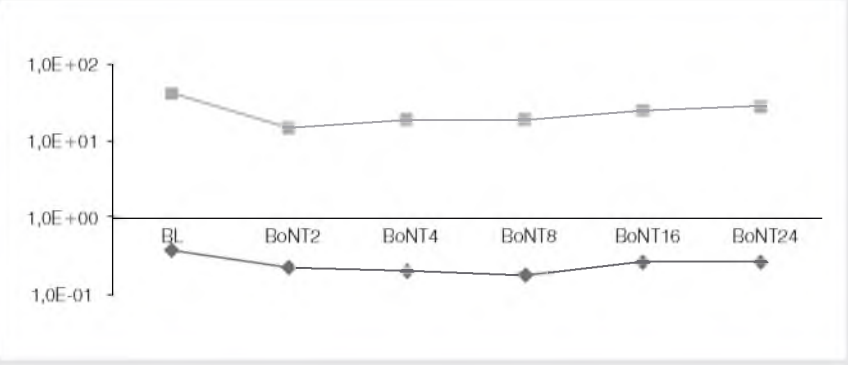
Data analysis included descriptive statistics; the median submandibular flow rates, the median DQs, and the largest salivary flow and DQ reduction were calculated. Unwanted effects and side-effects were tabulated at subsequent measurement moments. Nonparametric Wilcoxon signed-ranks tests were done for submandibular flow as well as for DQ to analyze differences in flow rate and DQ. According to our definition, two mucin activity measurements within eight weeks after BoNT-A injection were required. Missing mucin data were adjusted by "last observation carried forward" (LOCF) in which the last valid measurement was taken to replace a missing value or by a "worst case scenario" (WCS) in which the baseline measurement replaced the missing value. In addition,

multivariable analyses of variance (MANOVA) with a repeated measures structure were used to identify patterns of mucin response using the assessment points at two, four, and eight weeks as variables. For all statistics, a level of significance with one tailed p-values ≤ 0.05 was mandatory. All statistical procedures were carried out using SSPS 16.0 for Windows.

Results

All children were included in the analysis, as none of them dropped out. In all 17 children, we were able to measure the salivary flow rates and DQs at all assessment points. At baseline, data on mucin concentration were derived for all 17 children as well. The mucin concentration could also be calculated for 13 children at two weeks, for 12 children at 4 weeks, and for 14 children at eight weeks. The missing values occurred at different assessment points in different children. After treatment with BoNT, the median salivary flow rates and the median DQs were substantially reduced. Figure 1 shows the data of the median salivary flow rate and the DQ at consecutive assessment points. Eight weeks after BoNT application, a 50 percent reduction was seen in the median flow rate. Table 1

Figure 1 Median submandibular flow and DQ over time (N=17)



X-axis = assessment points over time; Y-axis = median submandibular flow on a logarithmic scale; DQ = Drooling Quotient; BL = baseline; BoNTx = Assessment points at x weeks after BoNT; = Drooling Quotient; = flow

shows the median of the flow and DQ over time. Compared to baseline, the median flow rates showed significant differences at all subsequent assessment points up to 16 weeks post BoNT application, except for the difference at four weeks post BoNT, which did not reach statistical significance. In addition, the median of the DQ measured at two, four, eight and 24 weeks also showed statistically significant differences compared to baseline. The parents noticed thickened saliva in nine children in the first eight weeks after BoNT application.

Table 1 Median flow rates and DQs between baseline and follow-up measurements

	Flow rate (range) (ml/min)	Sign[a]	DQ (range) (%)	Sign[a]
BL	0.38 (from 0.10 to 0.68)		42.5 (from 6.25 to 81.25)	
BoNT2	0.22 (from 0.04 to 0.66)	*0.017*	15,0 (from 0.0 to 65.0)	*0.003*
BoNT4	0.20 (from 0.06 to 0.96)	0.068	18.80 (from 0.0 to 62.50)	*0.009*
BoNT8	0.18 (from 0.04 to 0.54)	*0.001*	18.75 (from 1.30 to 58.75)	*0.007*
BoNT16	0.26 (from 0.04 to 0.46)	*0.002*	25.0 (from 0.0 to 65.0)	0.118
BoNT24	0.26 (from 0.08 to 1.46)	0.132	28.80 (from 0.0 to 81.25)	*0.036*

BL = baseline; BoNT= Botulinum Toxin; BoNTx = assessment points at x weeks after BoNT; DQ = Drooling Quotient; Sign = statistically significant different.

[a] non parametric two related samples test (Wilcoxon), two-sided p≤0.05; Italico = statistically significant different.

Swallowing and chewing were problematic in seven children, and two of these children, who had never been diagnosed with respiratory diseases needed treatment with mucolytics because of frequent coughing due to pooling of thickened saliva in the throat. Three children had swallowing problems within two

weeks after BoNT-A application and one child within one week. Another child had a dry mouth at night with an unpleasant oral odour. None of the parents mentioned any viscoelasticity problems at 16 and 24 weeks after BoNT injections (table 2).

Table 2 Results: side-effects

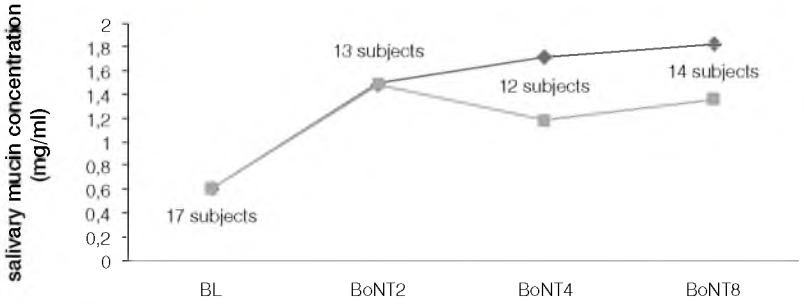
Number of patients	Thickening of saliva after BoNT-A injections	Swallowing/ chewing problems	Pooling of thickened saliva	Oral Odour
1	Within 8 weeks	+	-	
2	-	-	-	
3	Within 8 weeks	+	-	
4	-	-	-	
5	Within 8 weeks	+	-	
6	Within 1 week	+	+	
7	-	-	-	
8	Within 2 weeks	+	-	
9	Within 2 weeks	+	+	
10	-	-	-	
11	-	-	-	
12	Within 8 weeks	+	-	+
13	-	-	-	
14	-	-	-	
15	-	-	-	
16	Within 8 weeks	-	-	
17	Within 2 weeks	-	-	

BoNT = Botulinum Toxin; + = problems; - = no problems.

The individual salivary mucin concentrations differed between the children. Some children produced a small volume of highly viscous and sticky saliva which virtually completely remained absorbed onto the cotton rolls and could not be recovered for analysis. The values for the missing saliva samples (approximately 20% randomly missing) were substituted as mentioned above. A MANOVA with a repeated measures structure was performed to evaluate mucin concentrations over time. Using the LOCF scenario, significant changes in mucin concentrations over time were seen in the multivariable procedure (Pillais Trace F=6.552; df(3;14);

p=0.005/2). Huynh-Feldt adaptation was used to correct the degrees of freedom. The within subjects factor (mucin concentration) showed a trend indicating that the mucin concentration increased over time (F=6.677; df(1.4;22.2); p=0.01/2). Using the WCS, marginally significant changes in mucin concentrations over time were seen in the multivariable procedure (Pillais Trace F=2.492; df(3;14); p=0.103/2). This might imply that no effect over time in increase of mucin concentration could be shown. Inspection of the graphical representation and the Standard Deviations (SD) made clear that the variance in the measurements at two weeks post BoNT had increased (SD=2.562) compared to the variance in the baseline observation (SD=1.025). The mucin concentrations at four and eight weeks post BoNT remained constant on a higher level compared to baseline and their variances remained in the same range (SD = 1.383 and 1.536, respectively). Therefore, it may be concluded that the results from the WCS (F=2.597; df(3;48); p=0.063/2) coincided with the results from the LOCF analysis, indicating that the mean mucin concentration increased after BoNT treatment (figure 2).

Figure 2 Mean mucin concentrations over time (N=17)



X-axis = Assessment points; Y-axis = Mean salivary mucin concentration in mg/ml; BL = Baseline; BoNT= Botulinum Toxin; BoNTx = Assessment points at x weeks after BoNT;
◆ = Last observation carry forward scenario (LOCF); ■ = Worst case scenario (WCS); Subjects: number of observed subjects at each assessment point.

Discussion

From this prospective study, we can conclude that the salivary flow and DQ dropped effectively after injection with BoNT. We also observed that this positive outcome was accompanied by an increase in salivary mucin concentration. Therefore, this study supports the hypothesis that problems with masticatory and swallowing functions may be due to changing viscoelastic properties of saliva after Botulinum Toxin A treatment.

In the present study, sampling errors due to incorrect saliva collection methods were ruled out. The swab method proved to be a highly reproducible and reliable method in children with disabilities [18,19]. In addition, any differences in saliva composition between individuals due to circadian rhythms in flow and composition can be excluded [20]. It is possible, however, that some variability in salivary mucin concentration was caused by the swab method used, because the proteins in the saliva samples collected by this method are more variable compared to those from other saliva collection methods [21]. On the other hand, the distribution of salivary substitutes differs individually in general. Therefore, the wide distribution of the salivary mucin concentrations in our study population may be accepted as normal [22]. Furthermore, the rheological measurements in this study were accurate by using large flexible macromolecules, such as mucins, and their concentrations were calculated correctly [17]. The accuracy of the salivary flow rates based on the gauze weight method, however, may be diminished due to salivary density changes after administration of BoNT. The effect of these changes on the gauze weight method have not been investigated. However, the density of salivary protein is in the range of 1 promille. So it is reasonable to assume that in case of density changes the shift in protein content might be minor. Therefore, we think that the influence of the density changes did not hamper our findings. The main remaining limitations of this exploratory study are the small number and the heterogeneity of the participating children, as well as the short time of follow-up. Since approximately 20 % of the measurements were randomly missing, a sensitivity analysis was done using scenario studies to evaluate to what extent these missing data might have influenced the inferences drawn from the data. In the LOCF scenario, the last observation before the one missing was used to replace a missing value; in the worst case analysis, the baseline value was used to replace a missing value. Replacement by baseline values potentially causes a

serious "bias" towards the null, which implies that a type II error occurred. LOCF is a more realistic approach in which one assumes that no changes occur from one point in time to the next point in time. When comparing the result of these two analyses, statistically and according to content, we got an impression of the changes to be expected in these children over time. Notwithstanding methodological and power problems, the results of this study demonstrate a probable adverse effect after effective management of drooling with BoNT due to altered viscoelastic properties of saliva.

BoNT blocks the cholinergic (parasympathetic) component, which is responsible for the fluid discharge, with a concomitant increase in salivary substitutes concentrations. Former biochemical studies showed that Botulinum Toxin did not affect protein discharge [11,12]. However, previous studies focused on the effect of BoNT on salivary proteins such as secretory immunoglobulin A (immune system) and amylase (digestion), but salivary mucins, responsible for the rheological properties of saliva, have not been studied before [11,12]. In contrast to the secretion of the other salivary proteins, the secretion and the function of salivary mucins are dependent on water [10]. In case of dehydration, mucins might be secreted in plugs instead of a smooth film of mucus [23]. This phenomenon might by analogous to cystic fibrosis (CF) lung disease, in which altered fluid secretions across tracheal glands, an atypical mucin network with abnormal rheological properties, and altered mucus clearance may be responsible for airway "plugs" which are characteristic for the disease [24,25]. Thus, after management of drooling with BoNT injections, the ineffective salivary mucus film may cause more friction leading to incomplete wetting of the oral cavity and moistening of food which hampers mastication, swallowing, and speech.

It is hard to predict which children with CP and drooling treated with BoNT will have side effects due to thickened saliva. In normal subjects, the concentrations of salivary substances vary between individuals. This variability in salivary molecule concentrations precluded the use of saliva for diagnostic purposes to predict oral dysfunction [22]. This may also be the reason for the failure to show a correlation between the increased mucin concentrations and swallowing problems in the present study. On the other hand, it seems reasonable to assume that drooling CP children with the most severely disturbed coordination of tongue mobility and lacking voluntary control of lips, jaw, and tongue have insufficient strength to process the thickened saliva and have problems to clear the oral cavity.

The largest salivary flow reduction was achieved within eight weeks after botulinum application. This corresponds well with the time interval known from other studies [1,12]. The largest flow reduction coincides with the expectations that the clinical phenomenon of salivary thickening will appear in this period, just as in our population.

In conclusion, drooling can be treated effectively with BoNT injections. However, in some instances this may lead to thickened saliva causing mastication and swallowing problems. This study is the first to support the notion that the viscoelasticity of saliva changes after BoNT application. We observed that the swallowing function might worsen after BoNT injection in a group of children, of which most had CP but two intellectual disability. This work is relevant because it may be expected that the changed viscoelasticity influences the sensitivity of the mouth, the sensory perception, and the oral processing of food, and may have implications for oral health. In the management of drooling in children with CP, the risk of thickening of saliva after BoNT treatment should be taken into account. It is advisable to analyse the oral motor functions before treatment decisions. However, the supposition of changed rheological properties of saliva after submandibular Botulinum Toxin A application deserves further critical reflection and additional systematic studies.

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Part

8

Chapter

Botulinum Toxin assessment, intervention and aftercare for paediatric and adult drooling: international consensus statement

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Abstract

Many individuals with neurological problems or anatomical abnormalities of the jaw, lips or oral cavity may drool, which can impact on health and quality of life. A thorough evaluation of the patient's history, examination of the oral region by a speech pathologist and, in individuals over 3 years, a dental examination is warranted. Questionnaires with established validity such as the Drooling Impact Scale are useful assessment tools. A hierarchical approach to treatment is taken from least invasive therapies, such as speech pathology, to more invasive, such as injection of Botulinum neurotoxin type-A (BoNT-A) into the salivary glands (parotid and submandibular). The wishes of the individual and their carer are crucial considerations in determining the suitability of the intervention for the patient. In the presence of dysphagia and cerebral palsy (CP), careful assessment is required prior to the injection of BoNT-A. Favourable responses to intervention include a reduction in the secretion of saliva and in drooling, as well as psychosocial improvements. BoNT-A is usually well tolerated, although potential side effects should be discussed with the patient and carer.

Introduction

Drooling is one of the most significant problems impeding socialization, interpersonal relationships and integration into society for individuals with disabilities.[1-4] The constant presence of saliva may impair articulation and effective communication. The appearance and odour in combination with salivary spray when the individual talks or coughs results in social alienation. Drooling may cause health problems, the skin around the chin and perioral area may be chronically irritated causing troublesome rashes, and inadequate swallowing of saliva leads to aspiration, which may cause pneumonia. Individuals who drool may be perceived adversely with an underestimation of intellectual abilities and exclusion from normal peer activities.[4-8]

Objective

This is an international consensus statement defining the assessment, intervention and aftercare of patients with drooling treated with Botulinum neurotoxin type-A (BoNT-A) based on the best available evidence. The purposes of this evidence-based consensus document are to assist clinicians with the assessment, intervention and management of children and adults with drooling and to identify areas for future research based on gaps in the literature. These individuals have a range of underlying conditions. Literature was searched and appraised using a conventional evidence hierarchy. The highest levels of evidence available were used to develop recommendations, with randomized controlled trials (RCTs) and systematic reviews preferentially sought. Only when RCT or systematic review evidence was not available was lower level evidence and practice-based evidence included to answer clinical questions raised at the International BoNT Consensus Workshop. Expert opinion, where included, has been clearly labeled and should be interpreted with judicious caution. Recommendations for research were made based on the gaps identified in the literature. All recommendations were graded based on the American Academy of Neurology evidence classification.[9] The team that developed this document included a paediatrician, neurologist, speech pathologist, rehabilitation physician, and maxillofacial surgeon.

Definition

No generally accepted definition exists for the term 'drooling'. Drooling is also termed 'dribbling' and 'saliva loss'. Blasco's definition (1992) is often quoted: '*drooling is the unintentional loss of saliva and contents from the mouth*'.[4]

Salivation means the secretion or production of saliva. Normal salivation is poorly quantified but it is generally accepted that adults produce 1000–1500 ml of saliva per day.[10-12] Children prior to puberty produce significantly less (750–900 ml per day). Hypersalivation means the excessive production of saliva and is synonymous with sialorrhoea. No clear clinical criteria exist to describe hypersalivation or pathologic saliva production. In itself, an *overproduction* of saliva is of little clinical relevance if saliva *management* in the oral cavity is adequate. The majority of individuals with cerebral palsy (CP) produce normal amounts of saliva. There is some evidence that patients with Parkinson's disease (PD) produce less saliva than normal.[8,13]

The International Classification of Functioning, Disability and Health (ICF) refers to drooling as an impairment that involves disturbed intake of liquid (or solid) substances from the mouth to the digestive system. Although it correctly refers to the shortcomings in oral function or structure, this definition is not a useful description for clinical use.

With respect to aetiology and clinical impact, it is advisable to distinguish *anterior drooling* from *posterior drooling*. Saliva spilled from the mouth is referred to as anterior drooling, which is clearly visible. Posterior drooling is where saliva is spilled through the faucial isthmus creating a risk of aspiration.[14,15] Posterior drooling occurs in patients with severe oropharyngeal dysphagia.[16] Anterior and posterior drooling may occur at times in the same individual.

Aetiology

Drooling is normal in the growing child up to the age of 18 months. Beyond the age of 4 years, it is abnormal[5] and frequently persists in children with poor neuromuscular coordination, intellectual or learning disabilities, as well as in patients who have lost the structural integrity of their jaws, lips or oral cavity.[6] In addition, adults presenting with dysphagia with neurological disease such as

Recommendation 1

*Expert opinion.
In summary, the following is recommended:*
• To define the term 'drooling' as: the unintentional loss of saliva from the mouth
• That the terms anterior and posterior drooling should be distinguished

PD and motor neuron disease (MND) may have associated drooling.[7,8,17]
Drooling can vary from minute to minute depending on factors such as hunger, thirst, fatigue, anxiety, excitement and the circadian rhythm of saliva production over time.
It is widely accepted that drooling in CP is not caused by hypersalivation, but rather by oral motor dysfunction.[3] An exception to this may be for those with dyskinetic disorders where the abnormal movements may constantly stimulate the parotid glands to produce more saliva.[18]
The aetiology of drooling is multifactorial. In most individuals who drool, intraoral saliva management is disturbed to some extent. These individuals may demonstrate a variety of symptoms because of sensorimotor impairments, or there may be anatomical abnormalities.[18] Inadequate lip closure, habitual open-mouth posture, ineffective or limited tongue movements, poor coordination between the oral and pharyngeal stages of swallowing, malocclusion, flexed posture, gingivitis, and dental caries may contribute to the origin of drooling.[19,20]
In PD, there is evidence (Class III) that dysphagia, as a result of an impaired oral and pharyngeal stage of swallowing, positively correlates with drooling severity.[7,21]

Epidemiology

The prevalence of drooling has been infrequently studied, and the results cannot be compared as a result of variation in research design, patient selection, and data presentation. Quantification of salivary flow rate or drooling is challenging.[10]
In previous CP studies, about 10% of a Swedish population of children with CP showed 'embarrassing drooling'.[22] In another study, moderate to severe drooling

occurred in 10–37.4% of individuals.[23] Furthermore, the prevalence of drooling was investigated in a population of children with CP across dental age and of the total population, 58% had some degree of drooling (33% severe drooling, 9% moderate drooling and 16% mild drooling). The authors concluded that the degree of drooling decreased as the dental age increased.[24] A Spanish research group evaluated 50 individuals with CP, both children and adults, and 58% had drooling (mild in 44.4% and moderate to severe in 27.7%).[25]

Although no definite conclusion can be drawn from the literature, it seems reasonable to accept that one out of three individuals with CP drools to some extent. A recent study reported that drooling occurs in 70–80% of patients with PD.[10]

What is the best way to assess?

As drooling is a multifactorial problem, a range of assessments are required, undertaken, ideally, by a multidisciplinary team.

As drooling varies throughout the day, accurate measures have been difficult to achieve. Assessment begins with an investigation of the patient's goal for intervention, which may be for the purposes of social wellbeing. In the case of posterior drooling, a medical goal (no or less aspiration) can be defined.

The initial patient interview includes a thorough evaluation of the medical and social-emotional history of the patient and consideration of aetiology. Our approach is similar to that described previously (see Table 1).[26] Exclusion of upper airways obstruction is important. Some medications may be associated with excessive salivary secretion. Assessment by a speech pathologist is essential to consider trialling the most appropriate and least invasive oromotor interventions.

A dental examination is recommended for all individuals over the age of 3 years as carious teeth or poor dental hygiene can contribute to excessive salivary secretion. If BoNT-A is the preferred option, it is important to discuss realistic goals. This dialogue is informed by the clinician's understanding of the medical history and assessment of the patient's symptoms and their relative contribution to drooling.

A summary of recommended assessments is listed in Table 2. Measures that have been used to quantify salivary flow include the collection of saliva in bags or

Table 1 Assessment by members of a 'drooling team'

The team may include several of the following: dentist, ENT specialist, neurologist, nurse practitioner, occupational therapist, paediatrician, physiotherapist, plastic surgeon, psychologist, rehabilitation specialist, speech pathologist.
Assessment includes:
• Medical, social-emotional history of the patient, motivation, individual's ability to participate
• Medication (anticonvulsants, benzodiazepines, neuroleptic drugs)
• Respiratory status (cough, wheezing, recurrent pneumonia)
• Presence of allergy leading to a problematic increase in secretions
• Presence of gastro-oesophageal reflux, which, if severe, can be associated with hyperstimulation of the salivary glands
• Nutrition and hydration
• Neurological examination (alertness, cranial nerves, general motor skills/posture and tone)
• Orofacial examination (nasal breathing, upper airways obstruction)
• Oral hygiene, occlusion and dental health, dental examination
Assessment by a speech pathologist:
• Head control
• Mouth closure, occlusion, lip seal
• Oral sensorimotor examination (tongue lateralization, sensation, tone)
• Oropharyngeal stage of swallowing during eating and drinking (swallow on demand, frequency/efficiency)
• Speech (dysarthria/dyspraxia)
• Communication skills
• Management of secretions

chin cups (Lashley cup)[27,28] or by weighing bibs.[29] There are difficulties in ensuring accuracy with all these somewhat intrusive methods. These methods are more suited to research studies, along with the use of dental cotton rolls, suctioning saliva and, more recently, micropipette retrograde cannulation of major salivary gland ducts, which allows an accurate measure of flow and consistency. All of these methods measure the quantity of saliva secretion rather than the poor oral

Table 2 Recommended assessments

Assessment	Purpose	Who does it	ICF[a] domain measured	Properties	Clinical utility
[a]International Classification of Functioning, Disability and Health (ICF): valuable information can be found in the chapters about Body structures & Body Functions (S5, B5), Activity and participation (D7) and Environmental factors (E3). For children, the ICF-CY version should be reviewed.					
Speech pathologist exam	Examination of positioning, oral functions, speech and swallowing	Speech pathologist	Body structure: nose, dental, mouth, pharynx (s310–S330) Structures of head and neck region) (s710) Body function: sucking, biting, chewing, manipulation of food, salivation, swallowing (b5100–5105) Body function: speech, voice, articulation (b310–399)	–	Expert opinion to support decision making on treatment/ intervention
Drooling Quotient	Quantitative scores of drooling	Nurse/speech pathologist/ carer/teacher	Body function: salivation (b5104)	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

Drooling Impact (DrI) Scale	Questionnaire to assess the effect of saliva control interventions on drooling in children with developmental disabilities	Individual, carer or person who knows the individual well
Salivary flow	Measure saliva secretion in ml/min or g/min	Speech pathologist or any other well-instructed team member

Participation	Valid, reliable (test–retest), responsive to change	Free, no training required, <5 min to score, carer self-administered, over phone or in person
Body structure: salivary gland (s510)	Variable outcome with intra-and inter-individual variation, but reliable for research purposes with larger numbers of patients	Research purposes

motor control that is primarily responsible for drooling, although they may be useful as most treatments, such as BoNT and medication are designed to reduce salivary flow. More invasive techniques such as the use of radioactive isotopes have also been used but are contraindicated for safety reasons.[30]

A less invasive measure is the Drooling Severity and Frequency Scale (DSFS), which measures the severity, and frequency of drooling.[31,32] It gives an impression about the dimensions of drooling and can be used for studying outcomes. The ordinal scale makes it useful for statistical purposes. When the DSFS has been used for parent report after surgery[31], a greater reduction in severity than frequency has been reported, demonstrating lack of concordance with the patient's or caregiver's opinion.

Over the last few years, subjective questionnaires have been developed to record the views of the carer or patient.[33,34] If constructed carefully in relation to content and construct validity, they can be sensitive enough to reflect the concerns of parents or carers and to measure clinical change. One of these is the Drooling Impact Scale[35], which consists of ten items, rated on a 1- to 10-point scale. The individual patient, their carer(s), or someone who knows the patient well completes the questionnaire. The assessment reflects the changes in drooling as perceived by the person completing the questionnaire.

The measurement of drooling by observing the number of drips of newly formed saliva at the lips over a period of time and converting the result into a 'drooling quotient' (DQ) has also be trialled. This method is difficult to execute and has the prerequisite of a clear definition of drooling that is to be scored with precise time intervals. The DQ is a semi-quantitative observation method, which gives a number on a numerical scale reflecting the severity of drooling.[36,37] It may be used for research and clinical purposes.

For PD, there are two specific scales that may be helpful. Subheadings of the Unified Parkinson's Disease Rating Scale (UPDRS)[38] may be used, and the Sialorrhea Clinical Scale for Parkinson's Disease (SCS-PD) is a validated scale that specifically measures drooling related discomfort.[39]

Radiographic swallowing studies are available to study the separate phases of swallowing and to detect aspiration as an indication of 'posterior drooling'. These studies do not prove that posterior drooling is occurring but can suggest its presence and can be used in conjunction with a medical history of recurrent aspiration or pneumonia.

Which patients should be treated?

Recommendation 2

*Expert opinion.
A. A thorough assessment is recommended, and therapy based on:*
• A thorough evaluation of the medical and social–emotional history of the patient
• Examination of the oral region by the speech pathologist
• A dental examination in individuals greater than 3 years of age
• Questionnaires with good content and construct validity such as the Drooling Impact Scale
B. Assessment for research purposes may include additional measures, for example, the Drooling Quotient or the measurement of salivary flow.

Much information is available as to which patients might benefit from BoNT-A injected into the salivary glands, but few studies provide evidence of its effectiveness. Given it is an invasive procedure, there should be a significant problem with drooling for BoNT-A to be indicated, although there is an argument that drooling even small quantities can be socially disadvantageous and mitigate against successful integration into home, school and the community. The most important factor in determining whether a child or adult should be treated is the wishes of the individual or their carer to control the problem, with the hope of enhancing quality of life and participation.

Groups of patients that drool include those with CP; intellectual disability; acquired brain injury; neurodegenerative disease, for example PD and MND; post-cerebrovascular accident; oromandibular patients, for example those with head or neck carcinoma; sialadenitis; salivary fistula; and other more unusual neurological conditions, for example Moebius syndrome.[40]

The spectrum of conditions is obviously very wide, but there are potentially large numbers of individuals who could benefit from this treatment if it were more widely available.

Those that should be excluded

1. Individuals or carers who do not wish to control the drooling problem.
2. It is important that the clinician is aware as to whether BoNT-A has been used in other sites in the previous 4–6 months and works closely with other clinicians who may be injecting into other sites. Repeated injections within an interval of <3 months enhance the risk of antibody formation.
3. Patients unfit for anaesthesia or sedation, where these procedures are necessary for treatment. In adults, sedation is very rarely necessary for BoNT injection. Moreover, older children can sometimes be treated using local anaesthesia.
4. Patients that have developed antibodies to BoNT-A. These individuals may, however, be treated with an alternative BoNT formulation.

In our experience, the clinical development of antibodies is rare, as determined by the development of resistance to treatment, and the presence of antibodies does not consistently correlate with absence of effect.[41] If antibodies to BoNT-A develop, the use of BoNT-B can be considered.[42] In the presence of pre-existing swallowing problems, careful assessment and monitoring must be provided. Patients with pre-existing dysphagia, particularly those with CP and Gross Motor Function Classification System level V (GMFCS V), may be at higher risk for adverse events and must be assessed very carefully prior to injection.[43]

Potential alternative treatments:

1. Behavioural approaches
2. Medication
3. Oral appliances
4. Surgery

Timing of intervention

Little information is available to provide a recommendation about optimal timing, but there should probably be a 4- to 6-month time interval between each treatment. The manufacturer of BOTOX® advises a minimal interval of 3 months.[44] Gaining adequate saliva control prior to winter is important because drooling is an added burden in the presence of respiratory infections. It is important to define priorities with family members and clinicians who may be wishing to inject BoNT-A into other sites of the body.

Recommendation 3

*Expert opinion.
It is recommended that BoNT-A should not be administered:*
• If BoNT-A has been given for any reason in the previous 3 months
• If the patient has antibodies against BoNT-A
• If the patient is unfit for sedation or anaesthesia (this mainly relates to children as adults may have treatment without anaesthesia)
In the presence of dysphagia and CP with GMFCS level V, careful assessment should take place prior to injection.
Acquired resistance to BoNT therapy is a well-recognized phenomenon, marked by lack of beneficial effect. It is recommended that BoNT-B be tried after treatment failure with BoNT-A or vice versa.

What is the optimal Botulinum Toxin intervention regimen?

Rationale for treatment

Intraglandular delivery of BoNT-A inhibits the release of acetylcholine from cholinergic nerve endings and consequently reduces the secretion of saliva and diminishes drooling in the majority of patients.

Intervention options

Several prospective, controlled clinical trials have investigated BoNT-A and BoNT-B injections in the treatment of drooling.[17,35,45-55] A significant reduction in saliva was found using objective methods[47,50,56] (Class I) as well as subjective evaluations in these studies.[50,51,56] Supportive evidence for the efficacy of BoNT-A can be derived from two other articles.[57,58] In addition, BoNT-B has been shown to be equally effective and with similar side effects in a study of 30 children with CP or neurodegenerative disorders.[59] Injection sites include the submandibular gland, parotid glands or both and should be undertaken using ultrasound guidance to ensure delivery into the submandibular glands.[51,56,60] Recommendations for dosing and injection sites are outlined in Table 3. The use of ultrasound guidance for the parotids is also advisable, although experienced clinicians may rely on landmarks.[11,47,48,50,57]

Table 3 Injection site, dose and injection procedures[a]

[a] Different preparations are available e.g. BOTOX®, Dysport®, Myobloc®. All data reported here are from the published literature. BOTOX® and Dysport® are not exchangeable. Research suggests (level 3) that 1 Unit of BOTOX® equates to approximately 3– 4 Units of Dysport® but since the units are not interchangeable, to improve safety it is recommended that professionals follow manufacturer's dosing guidelines and do not use approximate conversions.

Injection Site	BOTOX®	Dysport®	Myobloc®	Injection Procedures
	U	U	U	
Submandibular gland	10–50	15–75	250–1000	Percutaneous injections, ventral approach, one injection/side, use of US, general anaesthesia (mainly in children)
Parotid gland	10–50	15–75	400–1000	Idem

Recommendation 4

*Expert opinion.

The following is recommended:

- Injection of BoNT-A into the salivary glands (parotid and submandibular) ideally under ultrasound guidance*

Tables 4 a,b list the Class I, II and III studies that have been undertaken in children and adults, respectively, to evaluate the efficacy of BoNT-A and BoNT-B.

Table 4 Evidence for use of Botulinum Toxin (a: paediatric drooling, b: adult drooling)

Reference	Design	Participants	Intervention	Outcomes	Adverse Events	Evidence (AAN)
a: paediatric drooling						
Alrefai AH *et al.* *Clin Neurol Neurosurg;* 2009[49]	RCT	*N*=24 (15 males, 9 females) Age: 21 months to 7 years CP & significant drooling	BoNT-A (Dysport®): 100 U or normal saline into the parotid glands bilaterally	Scores of median frequency ($P = 0.034$) and severity ($P = 0.026$) were reduced in the treatment group	Two patients in the active treatment group reported a transient increase in drooling after the injection	Class I
Banerjee KJ *et al.* *Dev Med Child Neurol;* 2006[61]	Clinical study without randomization. Drooling assessed at baseline, and 4 and 12 weeks	*N*=20 (10 males, 10 females) Age: 6–16 years CP & significant daily drooling (1 discont.)	BoNT-A: 2 U/kg; maximum 70 U; 1.4 U/kg parotid gland; 0.6 U/kg: submandibular gland	Drooling frequency and severity scores (Qualitative) significantly reduced at 4 weeks ($P < 0.001$) and 12 weeks ($P = 0.006$). QOL scores (Qualitative; rated by parents and teachers separately) significantly improved ($P < 0.001$ and $P = 0.023$ respectively). Number of bibs/ scarves changed per day (Quantitative) was significantly reduced at 4 weeks ($P < 0.001$).	No side effect from injections	Class III (pts are own controls)

Table 4 Continued

Jongerius PH *et al. Pediatrics;* 2004[45]	Controlled, open-label clinical trial	*N* =45 (28 males, 17 females) Age: 3–17 years; mean 9.5) CP & severe drooling Not previously treated with BoNT (6 discont.)	Single-dose BoNT-A (BOTOX®) injections (submandibular glands) versus scopolamine 30 U BoNT-A if <15 kg, 40 U if 15–25 kg, 50 U if >25 kg	Drooling reduced with scopolamine and with BoNT injections. Greatest reductions in DQ were achieved 2 – 8 weeks after BoNT. No sig diff (DQ) between scopolamine & BoNT injection during 24 weeks. VAS (parents): sig diff from baseline in all follow-up assessments. 'Success' (2-point decrease on TDS): 61.5% BoNT pts. Response rate (DQ) of 53% of pts to scopolamine and 48.7% to BoNT until 24 weeks	*Scopolamine* AEs reported in 82.2%: 5 (11.1%) mild, 14 (31.1%) moderate, and 18 (40%) severe AEs. Xerostomia (66.7%), restlessness (35.6%), somnolence (35.6%), blurred vision because of pupillary dilation, confusion (20%). *BoNT injections:* 2 (5.1%) transient flu-like syndrome (<2 days), 3 mild difficulty with swallowing.	Class II
Jongerius PH *et al. Neurology;* 2004[46]	Controlled clinical trial	*N* =45 Age: school aged CP with sialorrhoea	Single-dose BoNT-A injections (submandibular glands) vs scopolamine; 30 U BoNT-A if <15 kg, 40 U if 15–25 kg, 50 U if >25 kg.	Mean decrease in submandibular flow 25% during scopolamine, 42% following BoNT (from baseline). Response rates for BoNT were sig lower, varied from 69% at 2 weeks to 49% at 24 weeks after injection	4 pts discont. scopolamine due to AEs Mild incidental AEs reported from BoNT	Class II

Ong LC *et al. J Pediatr Neurol;* 2009[52]	Descriptive, open-label, non-blinded prospective trial	*N* =21 Age: mean age 8.4 ± 2.5 years CP	60–80 U BoNT-A (Allergan®); 15 U into each parotid gland; <15 kg 15 U, 15–25 kg 20 U, >25 kg 25 U into both submandibular glands	Improvement on DSFS, DQ, number of bibs changes per day, VAS, decrease in QoL scores within 16 weeks after injection	Pain and swelling, thick saliva, difficulty chewing in first 2 weeks after BoNT injection	Class III
Reid SM *et al. Dev Med Child Neurol;* 2008[35]	Prospective RCT; multicentre	*N* =48 (27 males, 21 females) Age: mean 11 years to 4 months, range: 6-18 years Drooling & CP & other neurological disorders	BoNT-A injections (25 U) into submandibular & parotid glands (tx *n* = 24), control: no tx)	Max response was at 1 month (assessed by carers using DIS); Highly sig diff in mean scores between groups at 1 month. This diff remained significant at 6 months, 4 children failed to respond to the injections, 4 had mediocre results, and 16 had good results	One child had difficulties with swallowing and deterioration of speech for 5 days following injection, another child developed a chest infection on day 5, and a third child had his first seizure 2 days post-injection	Class I
Savarese R *et al. Am J Phys Med Rehabil;* 2004[62]	Open-label, non-blinded, prospective study	*N* =21 CP & problematic drooling	15 U BoNT-A into each parotid gland.	Improvement on VAS, number of bibs used/day. Weight of dental rolls: 53% marked improvement, 11% no response	None	Class III

Table 4 Continued

Suskind DL *et al.* *Laryngoscope*; 2002[63]	Prospective open-label, dose-escalation study	*N* =22 Age: 8–21 years CP & sialorrhea	1st group (*n* = 12) injected into only the submandibular gland (10, 20 or 30 U BoNT-A) 2nd group (*n* = 10) injected into the submandibular (30 U) and parotid glands (20, 30, or 40 U)	All subjects successfully underwent BoNT-A injections. Objective 'drool quantification' with dental rolls extremely difficult. Most indicative of results was the "drool rating" questionnaire and the DQ	No local or systemic complications No adverse effects on swallowing	Class II
b: adult drooling						
Jackson CE *et al.* *Muscle & Nerve; 2009*[17]	RCT	*N* =20 ALS	BoNT B (Myobloc®) into parotid and submandibular glands; 500 U into parotid gland and 750 U into submandibular gland	Improvement on VAS and QoL scores; 50% of patients report improvement at 12 weeks post-BoNT	None	Class I
Kalf JG *et al.* *Parkinsonism Relat Disord;2007*[55]	Clinical study, independent investigator assigned to one of the groups using a list of random numbers	*N* =17 PD, UPDRS 2 points or higher, DSFS 3 points or higher	BoNT-A (Dysport®), total dose 150 MU 1st group injected into submandibular glands bilaterally 2nd group injected bilaterally in the parotid glands	Successful outcome: post-treatment score of 1 (slight) or 0 (normal) on the UPDRS drooling scale	Some side-effects: transient swallowing difficulties, xerostomia at night	Class II

Lagalla G *et al.* *Mov Disord;* 2006[50]	RCT	*N* =32 PD	50 U BoNT-A per parotid gland
Lipp A *et al.* *Neurology;* 2003[47]	RCT (Single-centre, prospective, double-blinded, placebo-controlled, dose-finding study)	*N* =32	BoNT-A (Dysport®) 18.75, 37.5, and 75 MU per parotid gland
Mancini F *et al.* *Mov Disord;* 2003[51]	RCT	*N* =20 PD	BoNT-A (Dysport®) 146.25 U per parotid gland; 78.75 U per submandibular gland
Ondo WG *et al.* *Neurology;* 2004[48]	Double-blinded placebo-controlled trial	*N* =16 (13 males, 3 females) Age about 70 years; duration of PD about 12 years	BoNT-B injections 1000 units at two sites into each parotid gland and 250 units at one site into each submandibular gland (total of 2500 units)

Improvement on VAS, UPDRS-drooling, dental roll weight compared to placebo	None	Class I
Primary end-point was achieved with 75 MU BoNT-A	No treatment-related AEs	Class I
Improvement on DSFS compared to placebo	None	Class I
Improvement on VAS. Global impressions of change Drooling Rating Scale. No change in UPDRS, head posture of dysphagia scale	Side effects mild and included dry mouth (3 patients), worsened gait (2 patients), diarrhoea (1 patient) and neck pain (1 patient)	Class I

Table 4 Continued

Porta M *et al. J Neurol Neurosurg Psychiatry;* 2001[64]	Open-label	*N* =10 PD, ALS, CP	Mean 27.7 U BoNT-A per parotid gland, mean 11.9 U per submandibular gland	Improvement on VAS	None	Class III
Racette BA *et al. Mov Disord;* 2003[53]	Open-label pilot study	*N* =9 Parkinsonism	1000 U BoNT-B (Myobloc®) into each parotid gland	Improvement of 2.4 points on VAS (from 0 to 4, where 0 indicated no drooling and 4 indicated worst drooling) Mean flow reduction of 42%.	Dry mouth, resolved within one month	Class III

Abbreviations; QOL, Quality of life; ENT, ear, nose and throat; Discont, discontinued; Tx, treatment; DQ, drooling quotient; VAS, Visual analogue scale; DSFS, Drooling Severity and Frequency Score; UPDRS, Unified Parkinson's Disease Rating Scale; BoNT, Botulinum toxin; Sig diff, significant difference; Pts, patients; AEs, adverse events; RCT, randomized controlled trial; DIS, Drooling Impact Scale; MND, motor neuron disease; CP, cerebral palsy; PD, Parkinson's disease

What are the optimal adjunctive interventions?

A hierarchical approach to treatment for poor saliva control is taken from the least to the most invasive treatments.[65] These treatments, which may be undertaken concurrently, commence with speech pathology (oral sensorimotor therapies, developing eating skills), occupational therapy and physiotherapy (posture and seating), psychology (behavioural programs), and dentistry (maintenance of oral health and appliance therapy). In certain parts of the world, there are intensive behavioural therapies available involving a psychologist, whereas in other places, behavioural advice is given by a range of health professionals (see Table 5).

Medication is sometimes trialled along with behavioural intervention and/or sensorimotor programs and may be provided when the drooling is causing the individual distress in social settings e.g. in the first year of school. Behavioural interventions directed at self-management (improvement in swallowing and wiping of the mouth), may be more effective when paired with medication to provide an opportunity for a child to experience positive feedback from having a dry chin. There is clear evidence to support short-term positive results from behavioural interventions; however, many studies are small in number, use a wide range of treatments and lack specificity in measures.[66] Although further studies are needed to provide evidence of long-term improvement, a start has been made to determine the efficacy of behavioural programs.[67] As BoNT-A injections provide short-term relief from drooling, repeated injections are unlikely to be a permanent solution, providing a challenge to develop other more long-term options.

What are the expected outcomes of Botulinum Toxin therapy?

A favourable response to intervention is improvement in pathophysiological aspects such as a reduction in the secretion of saliva and reduction in drooling. Psychological and sociological improvements may also be expected from intervention for drooling.

How should patients be monitored?

Before starting intervention, patients should be informed about the potential risks and adverse events associated with BoNT-A. It is usually well tolerated; however, side effects can occur. Efforts should be made to reduce or prevent these.

Adverse effects

- To avoid serious side effects, BoNT-A should always be injected under optimal conditions with the patient lying quietly (sedation or anaesthesia if needed) and under ultrasound guidance.
- Repeated injections may be needed, and therefore, pain and anxiety should be minimized.
- No fatal side effects have been reported in the literature. There are a multitude of potential side effects, and the patients should be carefully monitored.
- Possible adverse effects during or following the injection include the following:

Adverse effects relating to trauma at the site of the injection

- Pain (not severe) at the injection site either during the procedure, or because of gland swelling (hours) or haematoma formation (days) following the procedure
- Haematoma in the peri-glandular region caused by bleeding from the skin or subcutaneous tissue
- Intraoral blood caused by intraglandular/transductal bleeding
- Swelling of the gland caused by bleeding or injection of too large a volume of solution
- Swallowing problems caused by swelling of the gland, which usually resolves within 2 hours
- Infection
- Theoretical possibility of trauma to the facial nerve when injecting the parotid

Adverse effects relating to BoNT-A and BoNT-B

- Increased dryness of the mouth leading to problems such as manipulation of solid food
- Thickening of saliva because the water component is influenced by cholinergic blockade leading to an increase in the concentration of mucins and proteins
- Chewing and swallowing problems because of diffusion of BoNT-A into the surrounding muscular tissue. Careful attention should be paid to eating and drinking abilities during the week following injection. When injecting the parotid, diffusion of BoNT-A into the masseter muscle is possible, causing weakness in chewing
- Loss of BoNT-A because of intravascular injection (without systemic consequences because of the low dosages used; however, iatrogenic botulism has been reported in a single case)

Recommendation 5

*Expert opinion.
The following is recommended to avoid or limit adverse events with the use of BoNT therapy:*
• The use of ultrasound guidance during injections
• Observation of the patients for at least 2 hours following injection
• Regular contact with the patients or caregivers in the week following injection to evaluate swallowing problems
• Being aware of the possibility that thickening of saliva over time may occur which leads to swallowing and respiratory problems
• Moist or pureed food in the first week following injection

Future directions

Much work still needs to be carried out to improve the management of poor saliva control in both children and adults with disabilities. Improved diagnostic and therapeutic methodology utilizing real-time imaging modalities would assist in better defining the clinical problem and the outcomes of treatment. A better evidence base for oral sensorimotor techniques would be useful, along with improved methods for neuromuscular control of the upper digestive tract.

Specific pharmacological control of salivary gland function would avoid some of the adverse effects currently encountered when using anticholinergic therapy. In addition, endoscopic surgical ablation of major salivary gland tissue or autonomic ganglions associated with major salivary glands would avoid the lengthy and sometimes difficult surgical procedures that are now undertaken.

With regard to BoNT-A therapy, it is possible that there may be some long-term effects gained because clinicians have observed some shrinkage in the size of the salivary glands following repeated doses of the toxin. This needs to be studied in detail using a research protocol.

Table 5 Adjunctive interventions[66,68-72]

Intervention	Indications for use
Behaviour Management: aims to assist the person to learn to manage their own saliva independently e.g. by wiping their mouth[66,68]	Person can comprehend instructions, physically carry out the task and is motivated
Oral Motor Therapy: aims to establish or restore oral coordination for eating by: (1) Exercises & stimulation to the face and mouth provided to address coordination of oral movements & saliva control[69] (2) Specific practice of graded functional activities involving person, task and environment adaptations[70]	Limited chewing and swallowing skills; poor lip closure; inability to sense saliva in and/or outside the mouth
Oral Appliances e.g. ISMAR (Innsbruck Sensori Motor Activator & Regulator): aims to assist with jaw stability and develop lip and tongue control[71]	Good cognition; able to tolerate an oral appliance, good family support

Intensity of intervention	Classification of recommendation: standard treatment	Classification of recommendation: with BoNT-A
Optimal intensity is not known	Effective with some groups	Data unknown
Optimal intensity unknown	U Data inadequate Probably effective with some tasks	U Data inadequate
Daily – possibly for several years	Effective	Not known

Seating and Positioning: aims to adapt or modify a person's position to enable the upright sitting posture for eating, social interaction, hand function and mobility. The intervention involves prescription and manufacture of customized seating cushions within a wheelchair or stroller[72]	Inability to sit upright for safe swallowing, transportation, social interaction or hand use

B, probably effective; U, inconclusive

	Optimal intensity unknown	B Probably effective	U Data inadequate

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Chapter 9

Summary and General Discussion

Nederlandse samenvatting en discussie

Dankwoord

Curriculum Vitae

Appendix: Flowchart, List of publications linked to the thesis

Summary and General Discussion

The general aim of the research presented in this thesis was optimalisation/ refining ultrasound guided submandibular Botulinum Toxin (BoNT-A) treatment for drooling in children with cerebral palsy (CP), and to provide basic concepts into the mechanisms that underlie the drooling problem. CP is the most common cause of physical disability in childhood. Moreover, drooling is a common additional impairment hampering the ability of a child to realize his or her intrinsic developmental potential. At the time we started our research, submandibular BoNT-A injections proved to be effective for drooling control in children with CP, however it was unknown why in a number of children drooling control was not achieved after submandibular BoNT-A. Therefore, we carried out a prospective study in a historic cohort of 151 Dutch children with CP or with exclusively intellectual disability.

Chapter 2 describes relevant dysfunctional neuronal networks of swallowing in drooling. CP was used as a clinical model to illustrate the comprehensive framework crucial for coordinating oral motor and associated (upper and lower) gastrointestinal functions. The execution of the sensorimotor aspects of swallowing rely on functionally connected pathways between the (extra)pyramidal cortical motor planning regions, brainstem controlling centres, cranial nerves and lower motor neurons. The site and extent of the brain injury determine the extent of the dysfunction. Disturbances in the cortical part of this network result in clinical symptoms as oral tone regulation problems, dysfunctional oral control (particularly incomplete lip-closure, tongue protrusion, slow and stiff tongue movement, diminished oral suction), delayed initiation and segmented swallowing during attempted volitional movement. Dysfunctional pharyngeal components of swallowing [i.e. automatic components of deglutition, such as throat clearing, laryngeal closure tasks] tend to rely on subcortical networks. The ability to plan and coordinate swallowing with ventilation activity may also be impaired [for example, early inspiration after a thin liquid swallow or variable duration of the deglutition apnea] and is consistent with brainstem involvement. It can be concluded that the wide range of swallowing, respiration, drooling and GI problems can be understood through and are caused by (partial) disruption of these swallowing circuitries and the brain-gut axis. It can be concluded that dysphagia and drooling are frequently occurring symptoms and long-term

neurological sequelae. In our opinion and at early stage, particular note should be made to the important contribution of dysphagia and excessive drooling to the burden of the child with CP and his/her family. In addition, the younger brain is a highly dynamic structure with the capacity for profound structural and functional adaptation. We think formulation of rational prognostic statements and development of appropriate plans of management of dysphagia should be based on awareness of the topography of the brain injury. This approach could also provide valuable information for the development of more effective intervention strategies for dysphagia in future.

Chapter 3 reports on a case-control study. The aim of this study was to investigate whether drooling in children with CP in general and in CP subtypes might be caused by hypersalivation. Saliva was collected from 61 healthy children and 100 children with CP who drooled, of whom 53 had spastic, 42 had dyskinetic, and five had ataxic CP. Our study supported the finding that no hypersalivation exists in children with CP who drool in general. Although we did not find arguments for hypersalivation in the total CP group, clinically the drooling in dyskinetic CP appears to be a subgroup. The drooling is more intense probably due to hyperkinetic oral movements. With mechanical stimulation of the salivary glands in these children, the total daily saliva secretion (generally about 600mL) was increased by at least 200mL per day. The contribution in added saliva secretion of the parotid glands was twice as large as that of the submandibular glands. This can be a relevant phenomenon in the management of drooling. **Chapter 4** reports about the efficacy and durability of submandibular BoNT-A in 131 children. Follow-up data after 2 and 8 months were compared to baseline assessments to investigate the effect and durability of injection. A clinically notable response was found in 48.9% of patients, which was reflected in a significant mean reduction in the Drooling Quotient (DQ; 0-100%) from a baseline of 29% to 16% after 2 months and 19% after 8 months. The mean Visual Analogue Scale (VAS; 0-100mm) showed a similar pattern, falling from 81 to 53 mm after 2 months, but showing a noticeable return to baseline after 8 months. Patients who responded to treatment after 2 months demonstrated relapse after a median of 22 weeks. **Chapter 5** describes the efficacy of submandibular BoNT-A treatment for drooling and mechanisms underlying its responsiveness in 126 children, divided over three groups: children with spastic or dyskinetic CP, and children with intellectual disability only. The findings suggest that submandibular BoNT-A treatment for

drooling has similar effects across children with spastic or dyskinetic CP subtype, or those with intellectual disability only. **Chapter 6** describes the first attempt to reveal the contribution of body functions and structures (as defined by the International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY)) to the outcome of a BONT-A submandibular injections. After completing a thorough literature study, we identified that the following factors are suggested to contribute to drooling severity: head position, lip seal, voluntary control of tongue movements, control of voluntary movement functions, and mental age. All five investigated clinical factors seem logical to influence treatment outcome. For example head position and lip seal are influenced by gravity. The same reasoning also applies to movement functions which are clearly related to head position. Previous investigations demonstrate that tongue mobility is strongly correlated with drooling and drooling control. Therefore, it seems plausible that the ability to control the tongue is an important factor related to therapy outcome, following the factor quantity of saliva reduction. Moreover, the risk of oromotor impairment is raised by any degree of intellectual impairment and therefore the relationship between mental age and therapy outcome might be expected. However, the exploration of this five nominated clinical factors did not lead to a favorable conclusion in 151 children. The observations implied that other variables and unknown mechanisms (and interactions between them) need to be considered to predict the outcome of BoNT-A treatment. **Chapter 7** reports on the salivary viscoelasticity change after BoNT application. We observed that the saliva became sticky in some children after intraglandular botulinum application and assumed that sticky saliva may cause swallowing problems due to increased protein concentrations and changed salivary viscosity causing more friction. The seromucous submandibular glands secrete mucins which coat and protect the epithelial tissue of the oral cavity, and give the typical viscoelastic character to saliva. In view of the anticholinergic properties of BoNT, it is likely that the watery component of saliva will be reduced and that the concentration of mucins will increase post-BoNT injection. Therefore, the salivary mucin concentration was analyzed before and after BoNT. The submandibular flow was substantially reduced with a concomitant increase in mucin concentration within eight weeks after BoNT application (from 0.612 up to 1.830 mg/ml). Thickened saliva was observed in nine children, and swallowing and chewing were problematic in seven children. Two of these children needed treatment with mucolytics because

of pooling of thickened saliva in the throat. The findings illustrate that in making decisions about the use of BoNT, the risk of problems with masticatory and swallowing functions due to thickening of saliva after BoNT treatment should be taken into account.
It is important to establish the impact of drooling on health and quality of live. The last section, **chapter 8,** shows an international Botulinum Toxin Therapy *consensus statement* for drooling. It assists the clinicians with the assessment, intervention and management of children and adults with drooling.

Conclusions and future perspectives

This thesis offers new and relevant information about Botulinum Toxin Therapy type A (BoNT-A) for drooling in children with spastic and dyskinetic CP subtypes and children with exclusively mental disabilities. It is demonstrated that after submandibular BoNT-A injections, the drooling intensity is halved for almost 6 months in approximately 50% of the children with CP in general. Obviously, the CP subtype does not affect the efficacy of submandibular BoNT-A. Although submandibular injections of BoNT are effective for drool control, when making decisions about the use of BoNT-A, the risk of adverse effects (trauma relation to injection, problems with chewing and swallowing as a result of thickening of saliva after BoNT-A or because of diffusion of BoNT-A into the surrounding muscular tissue) should be taken into account.
Beyond any doubt, the factor quantity of submandibular saliva reduction contributes to drooling control, however variables related to handling of secretions seem important for the "functional efficacy" of BoNT-A. The discrepancy between observed local effect (i.e. decrease of flow) and the clinically reported "functional efficacy" (i.e. insufficient drooling control) remains to be proven.[1] Although in literature head position, movement control, voluntary control over the tongue and lips, and mental age[2-5] have been reported as contributing to drooling, we found no evidence for any influence of these variables on the level of response. When grouped together these factors cannot indicate or predict which of the children will be responders or non responders with the chosen level of response. Our study was the first step to reveal the apparently complicated issue of body functions and structures playing a role in drooling and its treatment outcome.

These observations imply that other variables and unknown mechanisms (and interactions between them) need to be considered to predict the outcome of BoNT-A treatment. Therefore, we have evaluated the relationship between reflex saliva secretion of the parotid gland and observed therapy outcome of submandibular BoNT. BoNT-A injections resulted in a substantial direct effect on submandibular flow and probably had an indirect effect on the saliva regulation mechanisms (peripheral sympathetic inhibition of the reflex salivary secretion; central regulation by the hypothalamic circuitries).[6,7] There is evidence that the Hypothalamic-Pituitary Axis activity is altered in children with neurological disabilities[8-10], and therapy outcome to submandibular BoNT-A seems to be influenced by compensatory strategies of the central circuitries responsible for saliva production as well.

Much work still needs to be carried out to improve the management of poor saliva control in children with disabilities. In this thesis the used swab method measured the quantity of saliva secretion rather than the poor oral motor control, which is primarily responsible for drooling. Improved diagnostic and therapeutic methodology utilizing real-time imaging modalities, e.g. surface electromyography (EMG) of the submental muscle group; ultrasonography or Haste MRI of the tongue movements during swallowing, might assist in better defining the clinical problem and the outcomes of treatment.

In addition, another point of interest regards the Drooling Quotient. In the study described in chapter 3 of this thesis, the VAS and the DQ show a strong relationship between the carer's perception of reduction in their child's drooling and the longitudinal changes in the DQ scores after the saliva-control intervention. Clearly, the findings imply that the DQ and VAS enable us to determine the clinical effect of BoNT-A for drooling control. Otherwise we recommend the use of the swab method for monitoring salivary flow reduction in future intervention studies.

Finally, given the costs of Botulinum Toxin, the potentially side-effects and the fact that anesthesia is needed, it is important to realize what factors might influence treatment outcome of Botulinum Toxin injections and formulate strict indications for this therapy. In addition, the exact role of behavioral treatment and the surgical procedures that are now undertaken for drooling control need to be specified to formulate a clinical decision making model for differential indication of treatment options across childhood.

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Nederlandse samenvatting en discussie

De optimalisatie van submandibulair Botulinetoxine type A (BoNT-A) behandeling om het kwijlen bij kinderen met een Cerebrale Parese (CP) te verminderen is het thema van dit proefschrift. CP is de meest voorkomende oorzaak van een lichamelijke handicap op de kindertijd. Naar schatting kwijlt 1 op de 3 kinderen met een CP pathologisch, waardoor de verdere ontwikkeling ernstig belemmerd wordt. Bij de start van het onderzoek wisten we dat met submandibulair BoNT-A therapie het kwijlen te verminderen was, maar was het niet duidelijk waarom bij een aantal van de kinderen het klinische effect onvoldoende was. Om dit te kunnen beantwoorden hebben wij een prospectieve cohort studie uitgevoerd waarin 151 Nederlandse kinderen met CP of met uitsluitend een verstandelijke beperking meededen.

In **hoofdstuk 2** geven we een visie hoe disfunctionerende neuronale netwerken van het slikken leiden tot kwijlen. CP is gebruikt als een klinisch model om het uitgebreide netwerk te illustreren dat verantwoordelijk is voor de coördinatie van de mondmotoriek en de gastro-intestinale functies. Een goede functionele afstemming tussen diverse (sub)corticale motorische gebieden, de controlecentra in de hersenstam, de hersenzenuwen en de lagere motorneuronen is een voorwaarde voor een adequate slikfunctie. Klinische symptomen, zoals orale tonusdysregulatie, onvoldoende controle over de gewilde mondmotoriek (in het bijzonder onvolledig lipsluiting, moeite met de tong uitsteken, trage of stijve tongbewegingen en verminderde orale suctie), een vertraagde slikinzet of juist gesegmenteerd slikken, worden vooral bepaald door de plaats en uitgebreidheid van de hersenschade in de corticale gebieden. Pharyngeale slikproblemen, d.w.z. juist moeite hebben met automatiseren of plannen van het slikken, zoals schonen van de keel of sluiten van de stembanden op het juiste moment, wijzen meer op schade in de subcorticale netwerken. Ook het vermogen om de slik met de ventilatie te reguleren kan verstoord zijn in CP. Zo kan het inademen op ongebruikelijke momenten tijdens het slikken plaatsvinden of kan de slikreflex zelf verstoord zijn wat kan wijzen op betrokkenheid van de hersenstam. Uit de review komt naar voren dat het brede scala van slik-, ademhaling-, kwijl- en gastro-intestinale problemen begrepen en veroorzaakt worden door (gedeeltelijke) verstoring van deze “brain-gut axis”. Het is overduidelijk dat het kwijlen symptomatisch is voor neurogene dysfagie en een veel voorkomend neurologisch restverschijnsel

is. Wij vinden dat ouders/verzorgers en artsen zich in vroeg stadium de grote gevolgen van een slikstoornis moeten realiseren.

Hoofdstuk 3 beschrijft een case-control onderzoek waarin onderzocht is of hypersalivatie een rol speelt bij het kwijlen van kinderen met CP. Bij 61 gezonde schoolkinderen en 100 kwijlende CP kinderen (53 spastische, 42 dyskinetische en 5 atactische subtype) werd speeksel verzameld. De conclusie is dat er geen sprake is van verhoging van de speekselsecretie bij kwijlende CP kinderen. Wel lijkt het kwijlen in de dyskinetische CP intenser, wat mogelijk veroorzaakt wordt door hyperkinetische orale bewegingen. Door deze mechanische stimulatie van de speekselklieren kan de totale dagelijkse speekselafscheiding (ongeveer 600 ml) verhoogd zijn met ten minste 200 ml per dag. De bijdrage van de verhoogde speekselsecretie van de parotisklieren is tweemaal zo groot als die van de submandibulaire klieren. Dit zou kunnen betekenen dat de aanpak van behandeling van het kwijlprobleem in deze subgroep mogelijk anders is.

Hoofdstuk 4 beschrijft de effectiviteit en duurzaamheid van submandibulair BoNT-A voor kwijlklachten bij 131 kinderen. Follow-up gegevens na 2 en 8 maanden zijn vergeleken met die van de baseline metingen om het effect en de duurzaamheid van de injectie te bepalen. Ongeveer 50% van de patiënten reageerden met een significante verlaging van het Drooling Quotient (DQ; 0-100%): voor de behandeling een gemiddeld DQ van 29% en 2 maanden resp. 8 maanden na behandeling een gemiddeld DQ van 16% resp. 19%. De Visual Analogue Scale (VAS; 0-100mm) toonde een vergelijkbaar patroon (daling van de VAS score van 81 naar 53 mm bij 2 maanden; een duidelijke terugkeer naar de uitgangswaarde na 8 maanden). Patiënten, die reageerden op een behandeling, toonden een terugval na een mediaan van 22 weken. In **hoofdstuk 5** onderzoeken we de effectiviteit van submandibulair BoNT-A therapie en mechanismen die ten grondslag liggen aan de responsactiviteit in 126 kinderen, verdeeld over drie groepen: kinderen met spastische of dyskinetische CP, en kinderen met uitsluitend een verstandelijke beperking. De bevindingen suggereren dat de effectiviteit van submandibulair BoNT-A voor alle groepen gelijk is. In **hoofdstuk 6** beschrijven wij de eerste poging om de bijdrage van de verschillende lichaamsfuncties en structuren (zoals gedefinieerd door de International Classification of Functioning, Disability and Health voor kinderen en jeugd (ICF-CY)) op het effect van een BONT-A behandeling te bepalen. Uit een literatuurstudie komt naar voren dat hoofdpositie, lipsluiting, vrijwillige controle over de tong, gewild bewegen en het

verstandelijk vermogen bijdragen aan de ernst van het kwijlen. Onderzocht is of deze variabelen ook een rol spelen bij het therapieresultaat van BoNT-A. De rol van de positie van het hoofd en de lipsluiting op therapierespons lijkt logisch, omdat zij beiden door de zwaartekracht beïnvloed worden. Dit geldt ook voor gewild bewegen. Immers om efficiënt te kunnen bewegen is een goede hoofdpositie en -balans een voorwaarde. Eerdere onderzoeken veronderstelden al een correlatie tussen de tongmobiliteit en kwijlen waardoor het aannemelijk lijkt dat tongcontrole een belangrijke factor is, die bijdraagt aan de therapie-uitkomst van BoNT-A. Ook kan een relatie tussen verstandelijk vermogen en therapie-resultaat verondersteld worden gezien de mondmotoriek bij toenemende ontwikkelingsproblematiek ernstiger verstoord is. Echter na exploratie bleken de vijf genomineerde factoren niet bijdragend te zijn aan het therapieresultaat. Dit betekent dat nog andere variabelen en onbekende mechanismen voorspellend zijn voor het therapieresultaat van BoNT-A. Om de effectiviteit van Botox therapie te verbeteren is nader onderzoek naar deze onderliggende variabelen in de toekomst noodzakelijk. In **hoofdstuk 7** wordt een eerste studie beschreven die de verandering van de visco-elasticiteit van speeksel na Botox aannemelijk maakt. Na BoNT-A wordt het speeksel bij sommige kinderen dikker van consistentie en neemt de wrijving toe, waardoor slikproblemen verklaard zouden kunnen worden. De submandibulaire speekselklieren scheiden mucinen uit die het epitheelweefsel van de mondholte beschermen en het typische visco-elastische aspect aan speeksel geven. Door de anticholinerge eigenschappen van BoNT neemt de waterige component van speeksel af, waardoor uiteindelijk de concentratie van de mucinen toeneemt. In onze studie hebben wij de mucine-concentratie vóór en na submandibulaire BoNT-A injectie geanalyseerd. Het blijkt dat binnen acht weken na een BoNT-A injectie de submandibulaire flow aanzienlijk vermindert met een gelijktijdige verhoging van de mucineconcentratie (gemiddelde concentratie van 0,612 mg/ml toenemend naar 1,830 mg/ml). Het speeksel dikte in bij negen kinderen en zeven kinderen hadden slik- en kauw-problemen. Twee van deze kinderen moesten worden behandeld met mucolytica, omdat het verdikte speeksel in de keel bleef plakken. Deze bevinding toont aan dat rekening gehouden moet worden met een verhoogd risico op slik- en kauwproblemen als gevolg van indikking van speeksel na BoNT behandeling.
In het laatste deel wordt nogmaals benadrukt rekening te houden met de gevolgen van het kwijlen op de gezondheid en de kwaliteit van leven. **Hoofdstuk 8**

rapporteert over een internationale Botulinetoxine therapie *consensus verklaring* voor het kwijlen. Mogelijk helpt het de clinici met de beoordeling, interventie en de behandeling van het kwijlen bij kinderen en volwassenen.

Conclusies en toekomstperspectieven

Dit proefschrift geeft nieuwe en relevante informatie over Botulinetoxine Therapie type A (BoNT-A) om kwijlen bij kinderen met spastische en dyskinetische CP of met uitsluitend een verstandelijke beperking te behandelen. Na een eenmalige submandibulaire BoNT-A injectie is bij ongeveer 50% van de kinderen de intensiteit van het kwijlen gedurende bijna 6 maanden gehalveerd. Het CP subtype lijkt de effectiviteit van submandibulair BoNT-A niet te beïnvloeden. Hoewel submandibulair BoNT-A een effectieve therapie is om het kwijlen te behandelen, moet toch rekening gehouden worden met bijwerkingen (gevolgen van een trauma door de injectie, problemen met kauwen en slikken als gevolg van indikking van speeksel na BoNT-A of spierzwakte als gevolg van diffusie van BoNT-A in het omliggende spierweefsel).
Zonder enige twijfel draagt de speekselreductie bij aan het verminderen van het kwijlen (direkt adaptief effect), echter omdat de therapierespons niet altijd even goed is, is het belangrijk om te weten welke variabelen nog meer van invloed zijn op de werkzaamheid van BoNT-A. Hoewel in de literatuur beschreven is, dat de positie van het hoofd, gewilde motoriek, vrijwillige controle over de tong en lippen, en de ontwikkelingsleeftijd bijdragen aan kwijlen[1-4], vonden we geen bewijs voor enige invloed van deze variabelen op de therapierespons van BoNT-A. Echter, onze studie was pas de eerste stap om naar de invloed van de verschillende lichaamsfuncties en structuren op het therapieresultaat van BoNT-A te kijken. Onze observaties impliceren dat nog andere variabelen en onbekende mechanismen (en interacties tussen hen) van invloed zijn op de therapie-uitkomst. Daarom hebben we ook de relatie geëvalueerd tussen mogelijke reflexspeekselsecretie van de andere grote speekselklier (parotisklier) en de therapie-uitkomst van submandibulair BoNT-A. BoNT-A injecties hebben een indirect effect op de speekselregulatie via perifere sympathische reflexinhibitie of door centrale regulering via de hypothalamus.[5,6] We zien inderdaad dat na BoNT-A behandeling de speekselsecretie van de parotisklier afneemt en mogelijk gebeurt dit door

perifere sympathische inhibitie. Echter bij sommige kinderen wordt de verminderde submandibulaire speekselflow maar (deels) gecompenseerd door enige stijging van de parotisflow. De hypothese is dat dit waarschijnlijk centraal gereguleerd wordt, waarschijnlijk door de hypothalamus. Wij denken dus dat therapie-effect van submandibulair BoNT-A ook beïnvloed kan worden door gedeeltelijke toename van de speekselsecretie van de parotisklier. Het is duidelijk dat nog veel werk verzet moet worden om de behandeling van kwijlen bij kinderen met een handicap te optimaliseren. De in dit proefschrift gebruikte swabmethode meet de speekselsecretie in plaats van de slechte orale motorische controle wat uiteindelijk primair verantwoordelijk is voor het kwijlen. Wij verwachten dat verbeterde diagnostische methoden, zoals het gebruik van real-time beeldvorming, bijvoorbeeld oppervlakte elektromyografisch (EMG) onderzoek van de submentale spiergroep, Haste MRI of echografie van de tong tijdens het slikken, kunnen helpen bij het beter in kaart brengen van het klinische probleem of te wel de aard en ernst van de slikstoornis. Wij denken dat hierdoor de resultaten van de behandeling weleens zouden kunnen verbeteren.

Voorts willen we hier een opmerking maken over het gebruik van het Drooling Quotient. De VAS en DQ, beschreven in hoofdstuk 3 van dit proefschrift, tonen een sterke relatie tussen de perceptie van de verzorger over de vermindering van het kwijlen en de longitudinale veranderingen in de DQ scores na de BoNT interventie. De bevindingen impliceren dat de DQ en VAS ons in staat stellen om in de klinische praktijk het effect van BoNT-A therapie adequaat te vergelijken. Daarentegen moet de swabmethode voortaan alleen nog gebruikt worden in interventiestudies om de speekselreductie te monitoren.

Tot slot, gelet op de kosten van Botulinetoxine behandeling, de bijwerkingen en het feit dat steeds anesthesie nodig is, is het onontbeerlijk om inzicht te hebben in factoren die mede van invloed zijn op de effectiviteit van de BoNT-A behandeling. Dan pas wordt het mogelijk om strikte indicaties voor deze therapie te formuleren. Bovendien moet de precieze rol van de gedragstherapeutische behandeling en de chirurgische ingrepen, die nu worden uitgevoerd om het kwijlen te behandelen, gespecificeerd worden, zodat uiteindelijk een klinisch besluitvormingsmodel voor gedifferentieerde behandelopties voor de kindertijd geformuleerd kunnen worden.

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Corrie

Curriculum Vitae

Corrie Erasmus werd op 24 februari 1968 geboren te Amersfoort. In 1986 behaalde zij haar ongedeeld VWO diploma te Amersfoort (Eemland College). Van 1986 tot 1993 studeerde zij Geneeskunde aan de Universiteit van Amsterdam. Aansluitend was zij tot september 1995 AGNIO Neurologie in het Medisch Centrum Alkmaar (dr. R. ten Houten). Vanaf september 1995 was zij als AGNIO Neurologie werkzaam in het Canisius Wilhelmina Ziekenhuis te Nijmegen en startte in 1997 daar de opleiding klinische Neurologie (opleider dr. C.W.G.M. Frencken). De laatste 6 maanden van de medisch specialisten opleiding maakte ze in het UMC St Radboud af als fellow kinderneurologie (opleider Prof. dr. J.J. Rotteveel). Vanaf 1 januari 2005 is ze geregistreerd kinderneuroloog en staflid in het UMC St. Radboud. Haar belangrijkste aandachtsgebied is slikstoornissen als gevolg van neurologische aandoeningen op de kinderleeftijd en is zij coördinator van het slik/droolingteam kinderen dat internationaal bekend is. Het slik/droolingteam is een multidisciplinair samenwerkingsverband tussen de afdelingen kinderneurologie, revalidatie, KNO en orthopedagogiek van het UMC St Radboud/Sint Maartenskliniek in Nijmegen. Ze gaf vervolg aan het promotieonderzoek van dr. P.H. Jongerius (*Botulinum Toxin Type-A to treat drooling [2004]*) en in 2007 kon ze starten met het promotieonderzoek gericht op de verfijning van de Botox therapie voor drooling. In de tussentijd is het wetenschappelijk onderzoek serieus uitgebreid met het in kaart brengen van slikstoornissen bij kinderen met een neuromusculaire ziekte.

Op dit moment bestaan haar taken, naast wetenschappelijke activiteiten, uit patiëntenzorg binnen de afdeling Neurologie/Kinderneurologie, en onderwijs binnen het curriculum Geneeskunde. Corrie is getrouwd met Peter Stins en samen hebben zij drie kinderen (Anne en Bram [juni 1999] en Luuk [maart 2002]).

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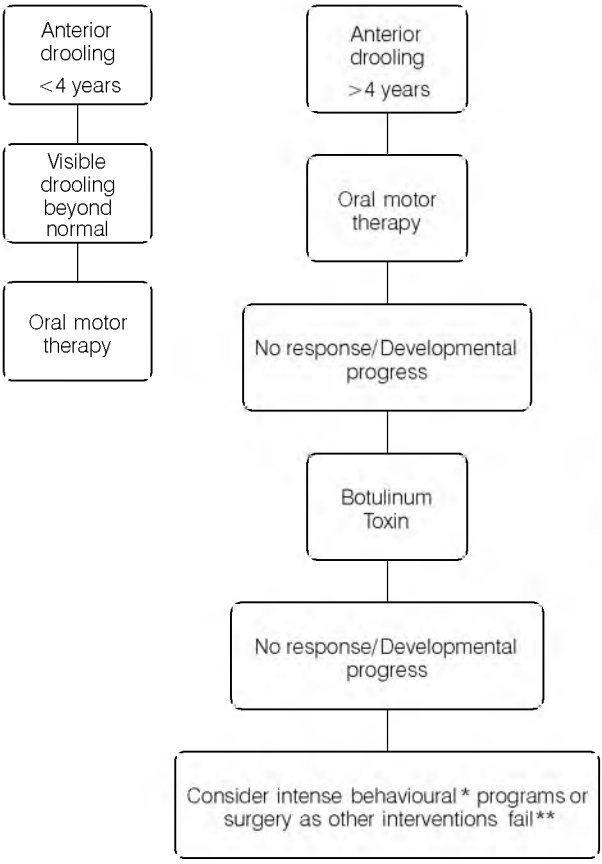
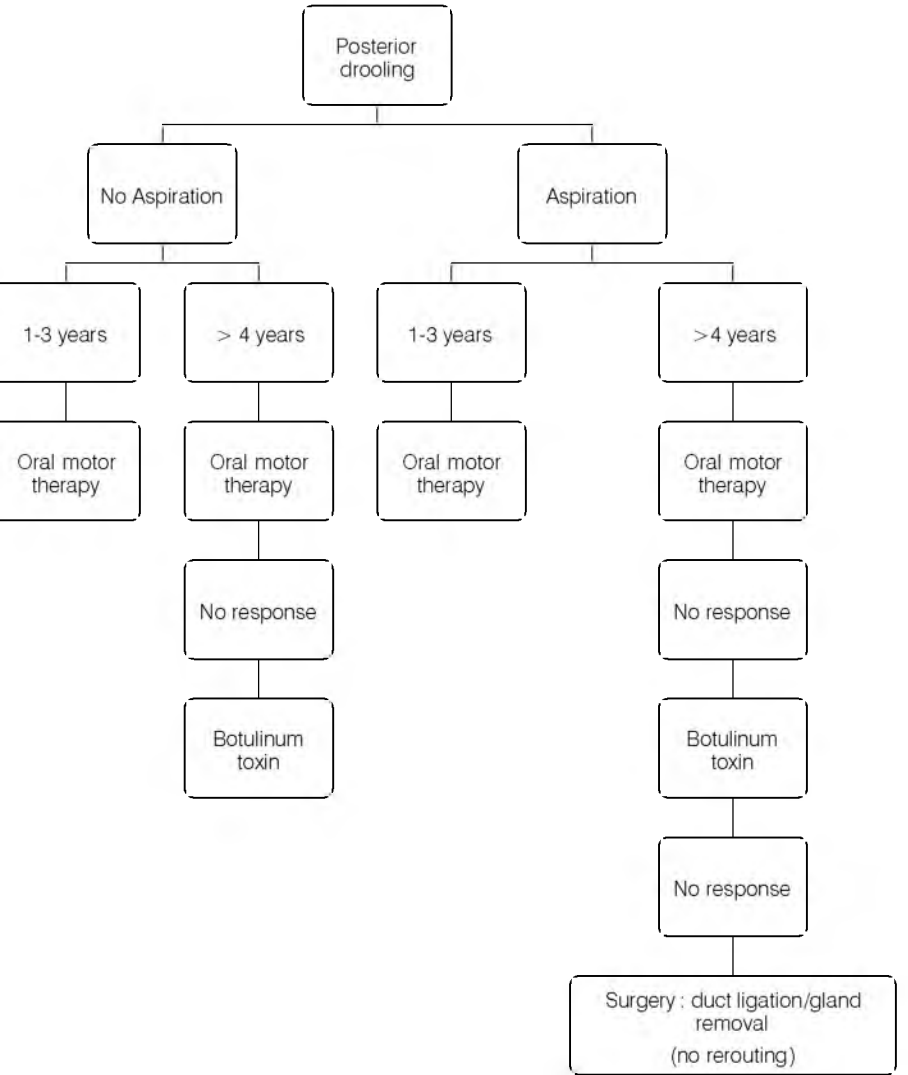


* van der Burg et al (2009)

** Scheffer et al (2010)


Posterior drooling
No Aspiration
Aspiration
1-3 years
> 4 years
1-3 years
>4 years
Oral motor therapy
Oral motor therapy
Oral motor therapy
Oral motor therapy
No response
No response
Botulinum toxin
Botulinum toxin
No response
Surgery : duct ligation/gland removal
(no rerouting)