Botulinum neurotoxin-A for drooling in children

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LIST OF ABBREVIATIONS

BoNT …… Botulinum neurotoxin

BoNT-A …… Botulinum neurotoxin-A

BoNT-B …… Botulinum neurotoxin-B

CP ……...…Cerebral palsy

DI ……...…….Drooling impact

DRS …….Drooling rating scale

DQ ……. Drooling quotient

DSFS ……. Drooling severity and frequency scale

FDA …… Food and drug administration

HC …….. Heavy chain

LC ……Light chain

MND ……Motor neuron disease

PG ……....Parotid gland

SLG …….……....Sublingual gland

SMDR ……..…Submandibular duct relocation

SMG …… Submandibular gland

SNAP ……Synaptosomal-associated protein

SNARE ……Soluble N-ethylmaimide sensitive fusion attachment receptor proteins

VAS ……Visual analogue scale

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ABSTRACT

Background: Sialorrhea, also known as drooling, hypersalivation or ptyalism, is often associated with neurological disorders or anatomical abnormalities in the oral cavity. It is also observed in up to 40% of children with cerebral palsy (CP). This condition may cause dehydration, skin erosion, and infection. There are three different serotypes of botulinum neurotoxin-A (BoNT-A) used clinically to control sialorrhea, all injected into the salivary glands, and associated with potential side effects. In December 2020, the Food and Drug Administration (FDA) approved for the first time IncobotulinumtoxinA (Xeomin®) for the treatment of chronic sialorrhea in children.

Objectives: The objectives of this thesis are: (**I**) to review the anatomy of the salivary glands and the pathophysiology of drooling in children, (**II**) to perform a systemic review and meta-analysis to evaluate the efficacy and adverse side effects of BoNT-A in children.

Methods: A literature review was performed to understand the factors contributing to drooling in children. A systematic review and meta-analysis were done to investigate the efficacy of BoNT-A treatment in children to reduce or improve the frequency and severity of drooling in children. Total drooling scores was the primary outcome measure.

Results: Four databases (Cochrane library, Embase, Medline and PubMed) were systematically searched. Out of 535 identified records, 21 studies met the inclusion criteria for the systemic review, and the meta-analysis was conducted on nine eligible studies involving 155 patients. A significant reduction in the frequency and severity of drooling was observed comparing children

before and after BoNT-A injections. BoNT-A was found to significantly decrease the severity of drooling in patients with sialorrhea (standardized mean difference [SMD], −2.06; 95% confidence interval [CI], −2.83 to −1.29; P<0.0001) when compared with the conditions before injections using random effects models. Six studies out of 21 reported dysphagia as adverse side effects after injection with minor other adverse effects like, thickness of saliva and pain at the site of injection. All of these adverse side effects were mild to moderate in range and transient.

Conclusion: BoNT-A injection into salivary glands is a clinically effective therapy that decreases drooling severity in children with sialorrhea. Also, despite some reported minor adverse side-effects, BoNT-A was shown to be safe. Future studies will need to further evaluate injection techniques, compare different BoNT-A serotypes, and examine dosages required to achieve optimal outcomes.

Keywords: *Sialorrhea, Botulinum Toxin-A, BoNT-A, Children, Drooling.*

RÉSUMÉ

Introduction: L'hypersialorrhée, également connue sous le nom de bavage ou hypersalivation, est souvent liée à une pathologie neurologique ou à une anomalie anatomique de la cavité buccale. Jusqu'à 40% des enfants atteints de paralysie cérébrale sont concernés par le bavage. Celui-ci peut-être à l'origine de déshydratation, d'érosion ou d'infection cutanée. Il existe trois sérotypes de toxines botuliques de type A (BoNT-A) utilisés en pratique clinique pour la prise en charge du bavage, tous sont injectés dans les glandes salivaires, mais présentent de potentiels effets secondaires. En décembre 2020, la «Food and drug administration» (FDA) a autorisé l'utilisation de l'IncobotulinumtoxinA (Xeomin^{R}) pour la prise en charge de la sialorrhée chronique de l'enfant.

Objectifs: Les objectifs de ce travail de thèse sont : (**I**) de synthétiser l'anatomie des glandes salivaires et la physiopathologie du bavage chez l'enfant, (**II**) de réaliser une revue systématique de littérature avec méta-analyse afin d'évaluer l'efficacité et les effets secondaires de l'injection de BoNT-A dans le cadre du traitement du bavage de l'enfant.

Méthodes: Une revue de la littérature a permis d'identifier et de synthétiser les particularités anatomiques et physiologiques impliquées dans le bavage chez l'enfant. Une revue systématique de littérature avec méta-analyse a été réalisée afin d'évaluer l'efficacité de l'injection de BoNT-A dans les glandes salivaires sur la réduction du bavage de l'enfant. La valeur du score de sévérité et fréquence du bavage a été utilisée comme critère d'évaluation principal.

Résultats: Quatre bases de données (Cochrane, Embase, Medline et Pubmed) ont été consultées. Sur les 535 articles identifiés, 21 ont été inclus dans la revue systématique de littérature et 9 dans la méta-analyse, représentant un total de 155 patients. Une réduction significative de la fréquence ainsi que de la sévérité du bavage a été observée en comparant les scores avant et après injection de BoNT-A. Nous avons mis en évidence une amélioration statistiquement significative du score de sévérité et de celui de la fréquence du bavage après injection de BoNT-A (différence moyenne standardisée (SMD), -2.06 ; intervalle de confiance (CI) à 95%, -2.83 à -1.29 ; $P<0.0001$) par rapport au score avant injection en utilisant des modèles à effets aléatoires. Six études parmi les 21 ont rapporté l'apparition d'une dysphagie comme effet indésirable après l'injection, ainsi que d'autres effets secondaires mineurs tels qu'un épaississement salivaire ou des douleurs au point d'injection. Tous ces effets indésirables étaient modérés à légers et temporaires.

Conclusion : L'injection de BoNT-A dans les glandes salivaires est un traitement efficace qui diminue la sévérité du bavage chez l'enfant. En outre, malgré quelques effets secondaires mineurs rapportés dans la littérature, la BoNT-A s'avère être un traitement sécuritaire. Il serait intéressant de réaliser des études complémentaires afin de standardiser la technique, comparer les différentes molécules de toxine botulique, ainsi que déterminer la dose qui permettraient d'obtenir des résultats optimaux.

Mots-clés : *bavage, hypersialorrhée, toxine botulique de type A, pédiatrie, hypersalivation*

CHAPTER 1

Introduction

1.1 Definition of the problem and rationale for study

In sialorrhea also known as anterior drooling, hypersalivation or ptyalism, saliva is visible beyond the margins of the lower lip. It is considered a normal physiological process under 5 years of age. Beyond this age, drooling may be associated with a pathological condition, typically caused by an incapacity to swallow saliva consistently and effectively, rather than an increase in salivary production (Daniel, 2012).

Salivary continence is a normal process of development of tongue and bulbar musculature, and it is achieved by 15-36 months. Swallowing saliva is a complex process that involves almost 25 pairs of bulbar muscles working together synergistically (Lakraj *et al*., 2013). Drooling has a prevalence of 0.6% in the general population and is more common in children with developmental or neurological co-morbidities such as cerebral palsy (Chaléat-Valayer *et al*., 2016). Drooling affects around 40% of children with cerebral palsy, causing significant physical and emotional morbidity as well as a significant influence on their everyday quality of life (Bekkers *et al*., 2020). Drooling for extended period can result in perioral maceration, fungal infection, and dehydration secondary to loss of fluids and electrolytes. Accumulation of saliva at the back of throat may lead to aspiration pneumonia which can be life threatening (Isaacson *et al*., 2020).

Treatment approaches for sialorrhea include conservative and non-conservative therapy. Botulinum neurotoxin (BoNT) injection is widely used to treat sialorrhea in children. Three different sub-serotypes of botulinum neurotoxin-A (BoNT-A) are available for the treatment of

excessive drooling, all associated with potential side effects. OnabotulinumtoxinA (Botox®) and AbobotulinumA (Dysport®) both are used off-label, to decrease saliva production in children who have issues with drooling. AbobotulinumtoxinA (Dysport®) is rarely used in children for treatment of drooling. OnabotulinumtoxinA (Botox®) is more frequently administered in children for treating drooling. IncobotulinumtoxinA (Xeomin®), perhaps because it is a purer form of BoNT-A without any additive protein. It was approved for the first time by Food and Drug Administration (FDA) on December 2020 for treating sialorrhea in children. Health Canada approved this drug only for adults on December 2020. Due to the absence of information about BoNT-A in the literature, it is important to conduct a study to evaluate the clinical benefits of BoNT-A and to compare different serotypes (e.g., Xeomin *vs*. Botox) in terms of effectiveness and adverse side effects to identify the best option available to treat drooling in children. This rationale has led to the objectives listed in the next section.

1.2 Objectives of this thesis

The aim of this thesis is to:

- (**I**) to review the anatomy and the pathophysiology of drooling in children.
- (**II**) to perform a systemic review and meta-analysis to evaluate the drooling frequency and severity of adverse side effects of serotypes of BoNT-A including OnabotulinumtoxinA (Botox®) and AbobotulinumtoxinA (Dysport®) in children.

1.3 Thesis organisation

Chapter 1 will identify the problem and state the objectives and goals of this thesis.

Chapter 2 will describe the essential anatomy and physiology of salivary glands, details about drooling, and treatment options, including a brief overview of BoNT.

Chapter 3 will present a systemic review and meta-analysis to evaluate outcomes of BoNT-A usage, assessed using the drooling frequency and severity measure, and assess adverse side effects of serotypes BoNT-A, including OnabotulinumtoxinA (Botox®) and AbobotulinumtoxinA (Dysport®) in children. This systemic review will highlight the need for future studies to determine which sub-serotype of BoNT-A is the best option to treat drooling in children.

Chapter 4 will present an overall discussion, including an outline of a potential clinical trial plan to compare three sub-serotypes (Botox *vs* Xeomin *vs* Dysport) .

Chapter 5 will contain an overall conclusion.

CHAPTER 2

Relevant anatomy and physiology of drooling

2.1 Salivary glands and saliva

The structures that discharge fluids to aid feeding appear gradually during evolution and can be seen in both, extremely simple organisms (e.g. *Caenorhabditis elegans*) and in more complicated species (e.g. *Drosophila melanogaster*) (Porcheri & Mitsiadis, 2019). Digestive fluids or protein rich fluids are synthesised and secreted by the major and minor salivary glands. There are two main group of glands, endocrine that leak products directly into the circulation and exocrine glands that secrete substances into a ductal system to an epithelial surface. Salivary glands belong to the exocrine class (Ghannam & Singh, 2019) and they are classified as major paired glands (parotid, submandibular, sublingual) (**Figure 2.1**) and minor salivary glands (**Figure 2.2**) located throughout the oral cavity within the submucosa of the oral mucosa (Kessler & Bhatt, 2018).

The parotid gland (PG) is the largest of all the three major glands extending from the mastoid tip to just below the angle of the mandible between the sternocleidomastoid muscle and the masseter (**Figure 2.1**). The stylomandibular ligament is the only thing that distinguishes the gland's inferior margin from the submandibular region from superficial to deep the gland is close to the facial nerve, which is a surgically essential location, then the retromandibular vein and the external carotid artery (Ghannam & Singh, 2019). The Stenson's duct is the principal excretory duct. It extends from the gland's anterior section over masseter penetrating the buccinator muscle and entering the mouth near the second maxillary molar tooth in the buccal mucosa (Carlson, 2000).

The submandibular glands (SMG) are in the submandibular triangle, the mylohyoid muscle separates the superficial and deep lobes of the glands (**Figure 2.1**). SMG is the second largest gland after the parotid gland. The primary excretory duct of submandibular gland, called as Wharton's duct enters the oral cavity via the lateral side of the frenulum linguae at the sublingual caruncle, emerging from the smaller, deeper lobe inferior to the mucosa of the floor of the mouth. Wharton's duct passes parallel and inferior to the hypoglossal nerve (Grewal & Ryan, 2020).

The smallest of three major glands is the sublingual gland (SLG). It is situated deep to the body of mandible and adjacent to the sublingual cavity (**Figure 2.1**). The main sublingual gland and 8-30 tiny minor sublingual glands make up the sublingual gland. The primary sublingual gland drains into the Wharton's duct, while the lesser sublingual glands drain onto the mouth floor via several rivinus ducts (Kessler & Bhatt, 2018).

The minor salivary glands consist of 800-1000 small salivary glands, present anywhere along the aerodigestive tract and on mouth floor. Every minor gland has one duct, they can be prominent when changed into mucous retention cysts and are otherwise hard to visualize on conventional imaging (**Figure 2.2**).

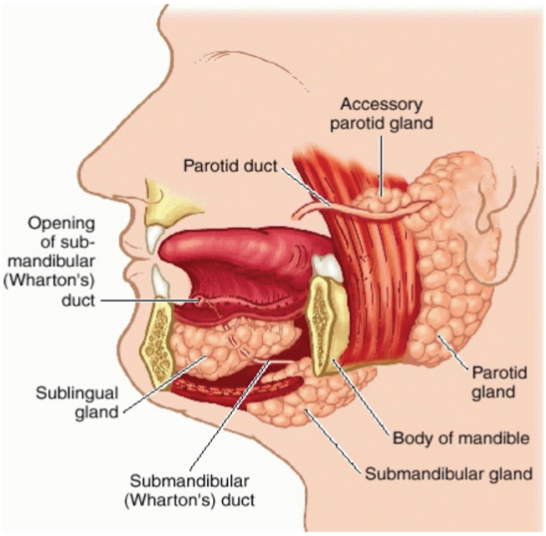

Figure 2.1: Major salivary glands and their excretory ducts. Human major salivary glands consist of three pairs of glands known as parotid, submandibular, and sublingual glands; together they are responsible for 90% of the total saliva. Adapted from *Dorland's Illustrated Medical Dictionary (p. 790), 2007, Philadelphia, PA: Elsevier. Reprinted with permission.*

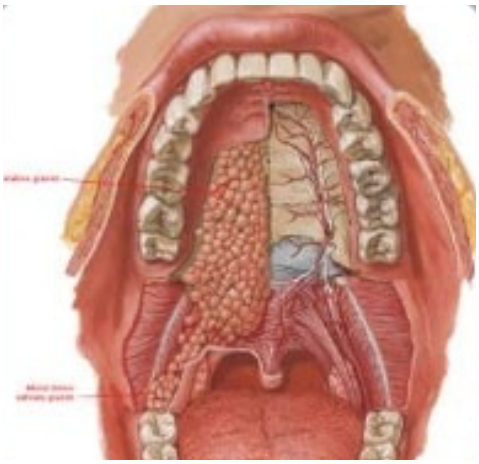

Figure 2.2: Minor salivary glands comprise ~800–1000 glands distributed throughout the oral cavity. Although they secrete <10% of the total secretion, this secretion serves as the main lubricant saliva due to its protective and mucous components. Adapted from *Dorland's Illustrated Medical Dictionary (p. 790), 2007, Philadelphia, PA: Elsevier. Reprinted with permission.*

Saliva is an acidic (pH = 6–7) complex fluid with a variety of physical, biological, and chemical qualities that influence oral health. The salivary glands generate between 0.5 and 1.5 litres of saliva every day, mostly produced by the three major salivary glands (92% to 95%). In the unstimulated state, the submandibular gland secretes the most of saliva about 70%, however under salivary gland stimulation the parotid gland produces more than 50% of the saliva (Möller *et al*., 2017), (Tiwari, 2011). Saliva contains 99% water, 0.3% proteins and both 0.2% inorganic and organic substances (**Table 2.1**) (Liu & Duan, 2012). The most prevalent inorganic components include sodium, potassium, calcium, magnesium, chloride, and carbonate, while the organic components comprise amylases, peroxidase, lipase, mucins, lysozyme, lactoferrins, kallikreins, cystatins, hormones, and growth factors (Chiappin et al., 2007). Salivary secretion is controlled by both the parasympathetic and sympathetic nervous systems. The saliva itself is produced in two types of acinar epithelial cells called serous cells, which secrete a watery fluid, and mucous cells, which produce a mucus-rich secretion (**Figure 2.3).** Serous cells are mainly found in the parotid gland, mucous cells dominate the sublingual gland, and there is a mixture of both in the submandibular gland. The secretory units merge into intercalated ducts, which are lined by simple low cuboidal epithelium, and surrounded by myoepithelial cells. The saliva moves from tiny ducts to larger ducts, eventually being released into the mouth. Besides the importance of saliva in homeostasis and immune protection, this biofluid has been utilised in diagnostics for over 2000 years (Tiwari, 2011), (Greabu *et al*., 2009), (Miletich, 2010). Recently saliva has taken a spotlight as a diagnostic and monitoring tool in many fields of science such as medicine, dentistry, and pharmacotherapy.

Table 2.1: Immunologic and nonimmunologic salivary content associated with essential functions of the saliva.

Functions	Immunologic and nonimmunologic salivary content
Antibacterial	IgA, IgG, IgM proteins, lectoferin, lysozyme, peroxidases
Lubrication	Mucin glycoproteins
Ionic reserve	Calcium phosphate, statherins, proline rich protein
Buffer	Bicarbonate phosphate, urea
Agglutination	Gylcoprotein, statherin, agglutinins, histidine rich protein
Food digestion	A-amylase
Gustation	Protein, Gustin, Zinc
Wound healing	Salivary histatins

Source: (Humphrey & Williamson, 2001).

2.2 Histology of salivary gland:

Three major cell types are found in salivary glands including, acinar cells, ductal cells, and myoepithelial cells. All salivary glands have the same basic structure of branching ducts that enter into the oral cavity and glandular secretory end pieces called acini that produce saliva (Ghannam & Singh, 2019). Acinar cells are divided into three types including, serous, mucinous, and sero-mucinous. Serous acini secrete a watery secretion, mucinous acini produce more viscous saliva rich in glycoprotein and mucin and both forms of secretions are seen in seromucinous acini. The quantity of each acinus in each of the major salivary gland differs and impacts the nature of their secretions (Triantafyllou & Fletcher, 2017). The parotid gland produces watery serous saliva and contains only serous acini. The submandibular gland contains a majority of serous acini with only 10 % of mucinous acini and sublingual gland has 90 % of mucinous cells (Holmberg & Hoffman, 2014). The ductal system plays an important role in modifying the electrolyte contents of the secretions. The intercalated, striated and excretory ducts are three primary types of the ductal

structures which are distinguished by their cellular makeup, location and function (Ghannam & Singh, 2019)

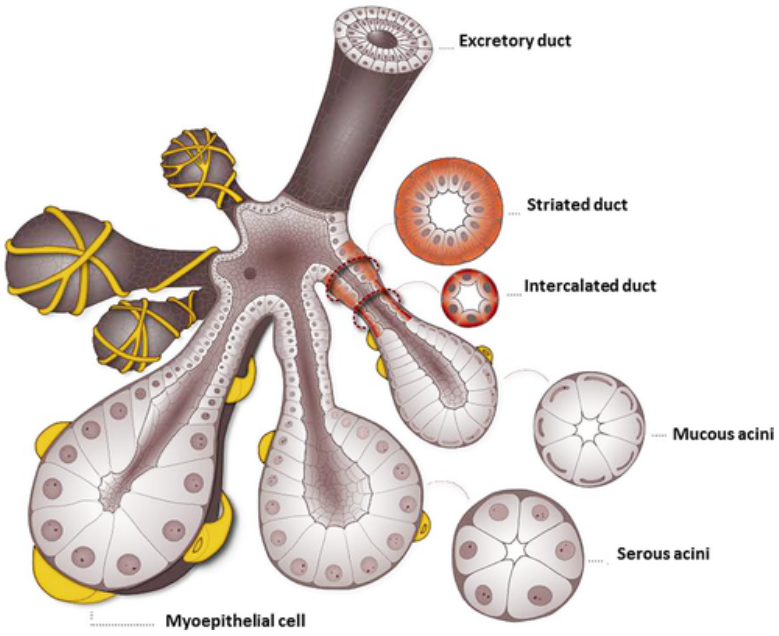

Figure 2.3: Schematic figure of fully developed salivary gland showing detailed parenchymal cells and their respective transversal section. This scheme illustrates a mixed secretory salivary gland composed of mucous and serous acini. Source: *Overview of Human Salivary Glands: Highlights of Morphology and Developing Processes, Reprinted with permission.*

2.3 Drooling

Anterior drooling, also referred to as ptyalism or sialorrhea, is the involuntary overflow of the saliva over the lower lip. It is considered normal during the development of oral bulbar musculature up to the age of 5 years, but beyond this age, drooling become pathological. Drooling is rarely secondary to hypersecretion of saliva. Most patients with drooling have difficulty in swallowing excess saliva due to the poor motor control of the oral musculature (Bavikatte *et al*., 2012), (Daniel,

2012). It is estimated 445,000 children under the age of 18 years are suffering from chronic sialorrhea in the United States and 30-53% of children with cerebral palsy experience drooling (Fairhurst & Cockerill, 2011).

2.4 Drooling etiology

Drooling is not a disease itself. Contributing factors for drooling including, lack of coordinated control of saliva by the oropharyngeal and tongue musculature, decreased perioral and intraoral sensory awareness, Inefficient or inadequate swallowing, dental malocclusion, mouth breathing (nasal obstruction, adenoid hypertrophy, allergic rhinitis), gastroesophageal reflux, side effects of certain medications (anticonvulsants, antipsychotics) and is often associated with neurological disorders, and motor impairments such as poor head and posture control(Lesperance & Flint, 2015).

2.5 Drooling classification

Drooling can be divided into two types, as anterior drooling, and posterior drooling. With anterior drooling, saliva dribbles from mouth over the lower lip and chin. This can leads to dehydration, perioral infection, and cause chipping of skin. Posterior drooling occurs when saliva penetrates laryngeal area which may lead to choking, gagging, vomiting, coughing. This can result in aspiration pneumonia. Severe posterior drooling can be life threatening. Disabled children who spend most of the day in a supine position have higher risk of posterior drooling (Bloem et al., 2009). Drooling can also be classified as acute (epiglottitis, peritonsillar abscess) or chronic (neurological reasons) depending on how long it lasts (Bavikatte *et al*., 2012).

2.6 Drooling measurements

There is no universal approved measuring technique for sialorrhea, which fluctuates as (occasional, frequent, or persistent) in terms of frequency and ranges from mild to profuse for severity measurements. Drooling has traditionally been measured using collecting devices such as urine or suction bags or radioactive isotopes. These approaches are time consuming and cumbersome, when utilizing a collection unit, leaking might be a concern. (Daniel, 2015), (Reid *et al*., 2010).

Several investigators weigh bibs, but this method is susceptible to measuring error due to evaporation, split beverages, and saliva missing the bib. Another objective measurement method for determining the frequency is the drooling quotient (DQ), which involves keeping track of each time drooling happens, throughout a 10-minutes period by recording the presence or absence of saliva every 15 seconds interval. This measurement does not consider the changes in volume and it needs extensive monitoring to achieve a reliable meaningful score, as drooling changes from time to time (Bothwell *et al*., 2002), (Ghezzi *et al*., 2000). Consequently, many clinicians have utilized alternative subjective measuring techniques in addition to the DQ. The drooling severity and frequency scale (DSFS) is the assessment tool which is based on a series of questions used to ask parents to score the severity and frequency of drooling (**Table 2.2**). This scale classifies the severity of drooling using a 5-level scale ranging from 1 (dry) to 5 (profuse drooling); and the frequency of drooling ranges from 1 (no drooling) to 4 (constant drooling) (**Table 2.2**). Additionally, another subjective approach used for measuring drooling is the weight and number of bibs changes each day (Thomas-Stonell & Greenberg, 1988), (Basciani *et al*., 2011).

A study conducted by Rashnoo & Daniel (2015) evaluated the use of different techniques for measuring drooling. They concluded that DSFS is a rapid and efficient tool for measurement of drooling that can be used to assist clinical management of drooling especially in individual who are not able to complete DQ assessment (Rashnoo & Daniel, 2015).

Table 2.2: Drooling severity and frequency scale (DSFS) measurement.

Severity	Frequency
1 = Never drools, dry 2 = Mild-drooling, only lips wet 3 = Moderate- drool reaches the lips and chin 4 = Severe- drool drips off chin & onto clothing 5 = Profuse- drooling off the body and onto objects (furniture, books)	1 = No drooling 2 = Occasionally drools 3 = Frequently drools 4 = Constant drooling

Source: *Treatment of sialorrhea in children with Cerebral Palsy: A double-blind placebo controlled trial* (Alrefai et al., 2009).

A recent study by Daniel *et al.* 2021, found that the number of bibs changed per day is an accurate predictor of sialorrhea that correlates positively with drooling severity and frequency despite the variability and lack of standardization in bibs. The study recommended that consistent definitions of what constitutes a bib, and its characteristics should be collected during drooling evaluation (Chen & Daniel, 2021).

2.7 Clinical assessment

The health consequences of drooling can be serious and potentially life-threatening. The presence of problematic drooling therefore has the potential to reduce the quality of life of both the child

and the wider family unit. In this way, the severity of drooling and its influence on the patients' and his/her family quality of life are used to determine the prognosis and manage the condition. Importantly, poor saliva control can also lead to reduced self-esteem and can affect the individual's successful integration into the community. Additionally, there are secondary impacts in caring for the child who drools, such as greater daily care demands and increased stress levels. Furthermore, it is common to identify oral lesions specially in the lip and chin. The patients' degree of awareness, swallowing abilities, motor skills and sensory abnormalities should be investigated during a neurological examination. In the same way, nutrition and hydration level, as well as the head posture and emotional state should be assessed (Bavikatte *et al*., 2012).

As mentioned before, in order to quantify drooling, objective and subjective measures have been used, such as counting the numbers of bibs used daily to contain excessive saliva production, measuring the weight of towels or dental cotton rolls to monitor saliva loss. Subjective scales such as the measurement of the drooling severity and frequency is available as a simple and comprehensive tool to use in the clinical setting (**Table 2.2**) (Güvenç, 2018), (Dias *et al*., 2016).

2.8 Treatment approaches

Drooling is a multidimensional condition that needs a multidisciplinary approach for clinical assessment and management. This can be accomplished by a teamwork involving a physician responsible for the medical history, physical examination, and therapeutic plan; occupational therapist who will work with specific devices (e.g., head-back wheelchair) to enhance swallowing and maintain proper posture; a dentist to evaluate oral and dental conditions such as malocclusion, tooth decay and gingivitis; and an otolaryngologist to assess macroglossia, and the upper airway

including adeno-tonsillar hypertrophy. A neurologist can also be a helpful team member depending on the conditions.

After a comprehensive evaluation, the management team, the patient, and the family should come to an agreement on the best treatment option. Management can be started in a progressive approach, beginning with the rehabilitative therapy, and progressing to pharmacotherapy and surgical options(Daniel, 2012), (Hockstein *et al*., 2004).

2.8.1 Rehabilitation treatments

Rehabilitation management options include posture and head control exercises, modifications to enhance positioning, oral motor or sensory training to promote oral control and awareness and behaviour therapy. To enhance the oral and facial muscle strength, oral sensitivity, awareness and motor skills, various oral motor and sensory therapies are used. Oral motor therapy can help with lip closure, tongue mobility and jaw stability. (Daniel, 2015).

Behavioural therapy can be useful in children with normal intelligence or minor intellectual impairments, using self-management procedure based behavioural interventions (de Bruijn *et al*., 2017). The purpose of behavioural therapy for drooling is to promote specific behaviours, like swallowing, wiping, increasing the duration of time being dry, closing the mouth, controlling the head position, and executing the self-management abilities. Behavioural therapy consists of four different techniques, including (i) instruction, prompting and positive reinforcement, (ii) negative social reinforcement and decelerative procedures, (iii) self-management procedures and (iv) cueing technique (Van der Burg et al., 2007).

2.8.2 Oral appliances and orthodontic treatments

Drooling can also be improved using variety of custom made oral devices that can help with lip closure. In some devices e.g, vestibular oral shield, Exeter lip sensor and palatal appliance, saliva can be redirect towards the pharynx by stimulating tongue movement with the help of devices. In patients with moderate drooling the use of beads in conjunction with swallowing therapy has proven to be effective (Hoyer & Limbrock, 1990), (Limbrock *et al*., 1991).

2.8.3 Surgical approaches

Surgical treatment of drooling is usually recommended for patients who failed to respond to rehabilitative and medical management, patients who are older than 6 years with moderate to profuse drooling, those who need chronic and continuous secretion management and serious complications from posterior drooling like aspiration pneumonia and choking may be managed by surgical treatment. Surgical treatment includes salivary duct ligation, salivary duct relocation and salivary gland excision. (Daniel, 2015).

Salivary duct ligation:

The simultaneous closure of bilateral parotid and submandibular duct (4-duct ligation) can be used as a minimally invasive, first line surgical approach for the treatment of drooling. The desirability of procedure lies in its simplicity, lack of apparent skin scar and absence of nerve damage with patient satisfaction (Panarese *et al*., 2001), (Chanu *et al*., 2012). Success rate ranges from 30% to 100% and relapse rates have been observed between 0% to 69% with recurrent time ranges from 3.5 to 9 month after surgery (Khan *et al*., 2016), (Hakim et al., 2008), (Stamataki *et al*., 2008). Overall salivary duct ligation appears to be a safe procedure. Complications reported include dry

mouth, increased risk of dental caries, delayed oral feeding resumption and aspiration pneumonia. Ranula development a common consequence of submandibular duct transposition has been mentioned by some authors (Khan *et al*., 2016), (Klem & Mair, 1999).

Salivary duct relocation:

Since the submandibular glands secrete about 70% of the resting saliva, they are an ideal target for surgical intervention in terms of saliva diversion. Hellen, first described submandibular duct relocation (SMDR) in 1969 and it has been demonstrated to be beneficial in 80% of children with a safe swallow. This technique is used to relocate the submandibular ducts to be the inferior pole of the palatine tonsil on both sides of mouth (Laage-Hellman, 1969). Kok *et al*. (2016) evaluated the consequences of SMDR on drooling and found that bilateral SMDR with removal of sublingual gland is the best surgical option for children (Kok *et al*., 2016).

Salivary gland excision:

Another surgical option for treating both anterior and posterior drooling is bilateral submandibular duct resection, as SMDR is not favourable for treating posterior drooling. Desling *et al*. 2015, examined 45 patients with neurological disability treated with this surgical procedure. The authors observed a 63% overall response rate and drastic improvement in subjective outcome measures after surgery (Delsing *et al*., 2015). **Table 2.3** shows surgical procedures for drooling with advantages and complications of each procedure.

Table:2.3: Surgical treatment procedures with advantages and disadvantages.

Type	Procedure	Advantages	Disadvantage
Salivary reduction	Nerve sectioning	Easily done under local anesthesia	High recurrence rate
	Ductal ligation	Simple	Sialocele or sialoliths
	Gland excision	Very good outcome	Xerostomia Complications such as facial, lingual, and hypoglossal nerve injury
Salivary diversion	Submandibular duct rerouting	Decreases anterior pooling of saliva	Ranula if sublingual gland is not excised Obstructive duct
	Parotid duct rerouting	Decreases anterior pooling of saliva	Obstructive duct and sialocele

Source: In Lesperance, M. M., & In Flint, P. W. (2015). Cummings pediatric otolaryngology. Reprinted with permission.

2.8.4 Medical treatments

Anticholinergic medicine like, scopolamine and glycopyrrolate were used as first line of medicine therapy for treating drooling. These drugs block the action of the neurotransmitter acetylcholine, blocking the parasympathetic innervation of salivary gland. Unfortunately, due to various side effects like, blurred vision, urinary retention and behavior changes these drugs present challenges when used in the treatment of drooling (Mier *et al*., 2000). **Table 2.4** represents the drugs used for drooling with dosages and side effects.

Table 2.4: Medical drugs used to treat drooling with the dosage and potential side effects.

Medication	Dosage	Side effects
Benztropine	Children ≥3 years: 0.02-0.05 mg/kg/dose 1-2 times daily Adolescents: 1-4 mg every 12-24 hours	Xerostomia Blurred vision Tachycardia Urinary retention Constipation
Benzhexol hydrochloride	Initiate at 0.1-0.2 mg/kg/day in three divided doses for 1 week; titrate gradually as required up to 2 to 3 mg twice daily	Xerostomia Dizziness Blurred vision Urinary retention
Glycopyrrolate	Children: Start at 0.02 mg/kg three times daily (maximum dose: 3 mg/day) Adults: 0.5 mg three times daily (maximum dose: 8 mg/day)	Xerostomia Blurred vision Irritability Behavioral changes Urinary retention Constipation
Scopolamine	1.5 mg transdermal patch once every 3 days	Xerostomia Blurred vision Irritability Dizziness Urinary retention Constipation

mg = milligram, kg = kilogram

Source: In Lesperance, M. M., & In Flint, P. W. (2015). Cummings pediatric otolaryngology. Reprinted with permission.

Botulinum neurotoxin (BoNT):

BoNT represents an interesting alternative for the treatment of drooling compared with systemic pharmacotherapy, and surgery. The bacterium, *Clostridium botulinum* and related species produce the neurotoxic protein known as botulinum neurotoxin - BoNT. There are eight different serotypes of BoNT, classified in alphabetically order from A to H and two of which (namely A and B) are used for medical purposes (Dutta *et al*., 2016), (Jost et al., 2019). Botulinum toxins are high molecular weight protein complexes consisting of the neurotoxin and the coat proteins (**Figure 2. 4**) The two chains of the neurotoxin are attached to each other through a disulfide bridge. The lighter neurotoxic section is a zinc-containing endopeptidase. The heavy chain connects to the presynaptic membrane of cholinergic terminal axons and ensures their uptake into the protein complex, whereby the lighter protein then attaches to proteins of the exocytosis complex (e.g., synaptosome-associated protein 25, SNAP-25) which inhibits the release of acetylcholine (**Figure 2.5**).

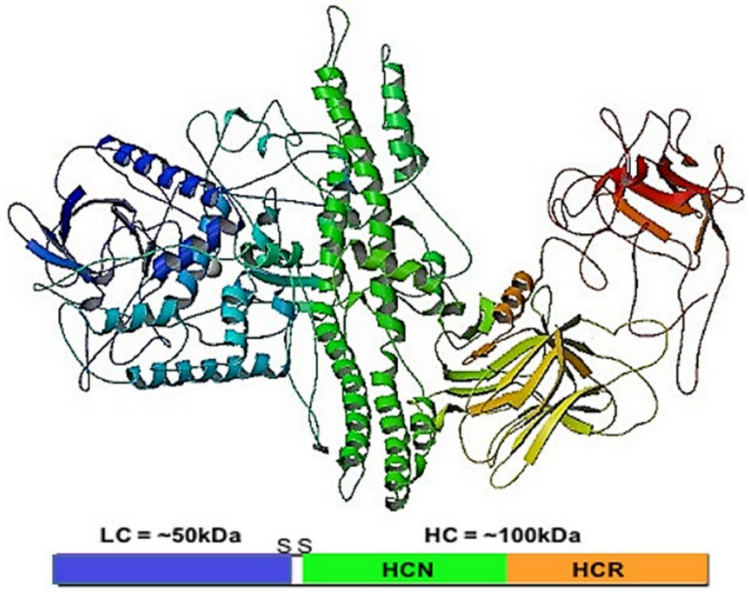

Figure 2.4: Botulinum Neurotoxin A (BoNT-A): The 50 kDa light chain (LC) (blue) is linked to the 100 kDa heavy chain (HC) (green, yellow, and red). The HC is functionally divided into the translocation domain (HCN) (green) required for transport of the LC from the endosome into the cell cytosol, and the receptor binding domain (HCR) (yellow and red) through which BoNT binds to the cell surface. Adapted from *Crystal structure of botulinum neurotoxin type A and implications for toxicity (Lacy et al., 1998). Reprinted with permission.*

Mechanism of action:

Cell entry by BoNT proceeds via a multi-step process (**Figure 2.4**). When BoNT is administered into gland tissue, it binds to glycoprotein structure on the cholinergic nerve terminal with remarkable specificity. The light chain of BoNT is then absorbed, cleaving various protein in the acetylcholine transport protein cascade (**S**oluble **N**-ethylmaimide sensitive fusion **a**ttachment protein **r**eceptor SNARE proteins) and transferring the cholinergic vesicle from the intracellular space into the synaptic cleft (Pellizzari *et al*., 1999).While BoNT is blocking the cholinergic

synapse, the nerve cell is creating new synapses to replace the old ones, this procedure is known as sprouting. Sprouting is simply a transient nerve process and while the sprouts are being destroyed, the original synapses are finally repaired. BoNT as a result only temporarily interrupts synaptic communications (de Paiva *et al*., 1999). Some researchers have proposed designating BoNT as a transient neuromodulator rather than a neurotoxin as it does not bring permanent changes in neural structure and function except synaptic blockage. BoNT inhibits the cholinergic autonomic innervation of salivary glands where effects may appear within 2-3 days and can reach at its peak level after two weeks. Injection of BoNT into glandular tissue can last up to 6 to 9 months (Dressler & Benecke, 2007).

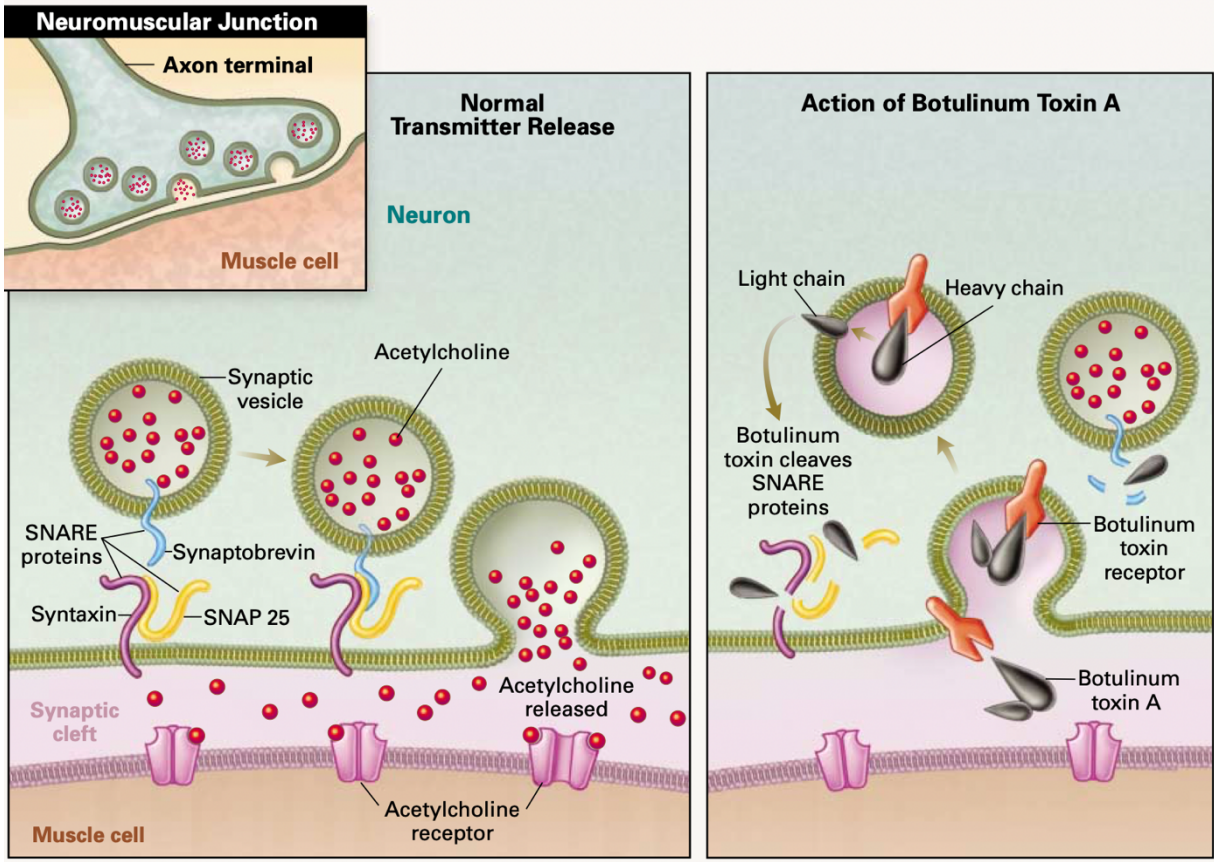

Figure 2.5: Mechanism of action of BoNT-A. (left side) shows how the neurotransmitter (acetylcholine) released from synaptic vesicle and reaches at receptors on muscle fiber which causes muscle contraction. (right side) shows light chain of BoNT cleaves specific SNARE protein which is responsible for formation of SNARE complex to release neurotransmitter. Thus inhibiting the transmission of acetylcholine resulting paralysis of muscle fiber. Source: *Rowland L. P. (2002). Stroke, spasticity, and botulinum toxin. The New England journal of medicine, 347(6), 382–383.* (Rowland, 2002). *Reprinted with permission.*

BoNT-A has been used for treatment of drooling in children. Three sub-serotypes (Onabotulinum/Botox, Incobotulinum/Xeomin and Abobotulinum/Dysport) have been specifically used for drooling (**Table 2.5**). Botox has been frequently used off-label for drooling in children for many years. In fact, it is the most used BoNT-A for drooling. Recently, in December 2020, the FDA approved Xeomin for the treatment of drooling in children. Xeomin is considered by some as a better option compared with Botox because it is a pure form of the toxin, without any additive protein and low molecular weight (150 kDA). In another way, Botox contains additional

albumin protein, with high molecular weight (900 kDA), and require refrigeration before usage (Frevert & Dressler, 2010), (Martínez-Poles *et al*., 2018). Rappl *et al*. 2013, conducted study using Xeomin for treatment for glabellar frown lines and they found it has more rapid onset and longer duration of treatment effect than another sub serotype of BoNT-A.

Table 2.5: Subtypes of BoNT-A available to treat drooling in children.

BoNT-A	Botox	Dysport	Xeomin
Manufacturer	Allergan (USA)	Ipsen Pharmaceuticals (FR)	Merz Pharmaceuticals (Germany)
Pharmaceutical preparation	Powder	Powder	Powder
Molecular weight	900 kDA	300-900 kDA	150 kDA
Composition	Toxin + albumin protein	Toxin + albumin protein	Pure toxin
Bacterium strain	Hall A	Ipsen srtain	Hall A
pH	7.4	7.4	7.4
SNARE Target	SNAP 25	SNAP 25	SNAP 25
Shelf life	24 months	15 months	36 months
Storage	Below 8^{o}C	Below 8^{o}C	Below 25^{o}C

USA=United states of America, Fr=France, pH= power of hydeogen, SNARE= Soluble N-ethylmaimide sensitive fusion attachment receptor proteins, SNAP = synaptosomal-associated protein, kDA= kilodalton. *Source: Modified from Dressler & Benecke (2007).*

2.9: Link to Chapter 3

In view of the above, there is a need to determine if BoNT-A has been effectively used previously to treat drooling. Chapter 3 does this by conducting systemic review and meta analysis on studies that reported use of all serotypes of BoNT-A for treatment of drooling inn children. In this review we will see about efficacy and potential adverse effects of BoNT-A.

CHAPTER 3

THE CLINICAL BENEFITS OF BOTULINUM TOXIN TYPE-A SEROTYPES FOR DROOLING IN CHILDREN: A SYSTEMIC REVIEW AND META-ANALYSIS

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3.1 Abstract

Introduction: Sialorrhea, also known as drooling or ptyalism can have a severe psychosocial impact on patients and their families. Three different serotypes of botulinum neurotoxin-A (BoNT-A) have been used for sialorrhea, but to date there is no consensus as to the best molecule to use.

Objectives: The objectives of this study are (a) to understand the clinical benefits of the use of BoNT-A for drooling in children. (b) to evaluate effectiveness of BoNT-A to reduce or eliminate drooling in children. (c) to assess the adverse side effects of BoNT-A in children.

Methods: Four databases (Cochrane library, Embase, Medline and PubMed) were systematically searched (up to 1 May 2021). A systematic review and meta-analysis were done to investigate the efficacy of BoNT-A treatment in children to reduce the frequency and severity of drooling in children. Total drooling scores was the primary outcome measure. The included studies consist of randomized control trials or controlled trials, prospective and retrospective studies.

Results: Out of 535 identified records, 21 studies were eligible considering the inclusion criteria. The meta-analysis was conducted on nine studies involving 155 patients. A significant reduction was observed in the frequency and severity of drooling, comparing the children before and after BoNT-A injections. BoNT-A was found to significantly decrease the severity of drooling in patients with sialorrhea (standardized mean difference [SMD], −2.06; 95% confidence interval [CI], −2.83 to −1.29; P<0.0001) when compared with the conditions before injections using random effects models. Six studies out of 21 reported dysphagia after injection with minor other adverse side effects, such as thickness of saliva and transient pain.

Conclusion: BoNT-A was found to be a clinically effective therapy for drooling in children. Reported adverse side effects were mild and transient. Future studies are needed to further evaluate the best injection techniques and to identify the ideal dosages required to achieve the optimal outcomes.

Keywords: Sialorrhea, Botulinum neurotoxin-A, BoNT-A, Children, Drooling.

3.2 Background

Sialorrhea, also known as drooling, hypersalivation or ptyalism, is often associated with localized anatomical abnormalitie or neurological disorders (Lipp *et al.*, 2003). The submandibular glands produce 65 to 70% of the saliva, the parotid glands 20 to 25%, the sublingual glands 5%, and the minor salivary glands another 5% (Blasco & Allaire, 1992). It is estimated that 30-53% of children with cerebral palsy experience drooling (Fairhurst & Cockerill, 2011).

The health consequences of drooling can cause serious physical and socio-emotional morbidity as well as a significant influence on the everyday quality of life of both the child and the wider family unit (Bekkers *et al*., 2020) (Leung & Kao, 1999). Drooling for extended periods can result in perioral maceration, fungal infection, and dehydration (Bailey & Wadsworth, 1985). The current treatment and rehabilitative options have limited clinical success in severe cases (Weissbrod & Merati, 2012), (Daniel, 2012). Pharmacotherapy and surgery have been shown effective but can have severe side effects such as Xerostomia (Mier *et al*., 2000).

Recently, botulinum neurotoxin (BoNT), has been used in the treatment of drooling in order to decrease the volume of saliva (Reddihough *et al*., 2010). BoNT inhibits the release of acetylcholine from cholinergic nerve terminals, causing glands to become inactive (Reddihough *et al*., 2010). Botulinum toxin A (BoNT-A) and botulinum neurotoxin B (BoNT-B) are the two serotypes of BoNT utilized in clinical practice to treat aesthetic and medical issues (Chinnapongse *et al*., 2012). There are three serotypes of BoNT-A available for the treatment of drooling, including Onabotulinumtoxin A (Botox®; Allergan Inc), Abobotulinumtoxin A (Dysport®; Ipsen Ltd), and Incobotulinumtoxin A (Xeomin®; Merz Pharmaceuticals) (Aoki *et al*., 2006). It is observed that there are differences regarding the efficacy and adverse effects of BoNT-A serotypes. However, due to the absence of consistent information in literature in pediatric population, there is a need to

conduct a comprehensive study to assess (a) the clinical benefits, effectiveness and (b) the adverse side effects of all subtypes of BoNT-A to treat drooling in children.

3.3 Methods:

The analyses were performed on data from previously conducted studies, so this study did not require ethical approval.

3.3.1 Literature search

A comprehensive review of the literature was conducted in Embase via OVID (1947 to present), MEDLINE (1946 to Present), The Cochrane Library, and PubMed and the full search strategy is presented in **Appendix A**. A citation management software (EndNote-20) was used to assemble results. The literature was searched with key words and subject headings [“Sialorrhea” OR “drooling” OR “hypersialorrhea” OR “polysialia” OR “ptyalism” OR “salivary hypersecretion” OR “salivation OR “sialorrhoea OR sialosis] AND ["botulinum neurotoxin" OR "Botulinum toxin A" OR "Incobotulinum" OR "Abobotulinum" OR "Onabotulinum" OR "Botox" OR "Dysport" OR "Xeomin"] AND [“newborn” OR “neonat” OR “infant” OR “children” OR “paediatric”]. The findings included, “treatment response”, “effective sub serotype” and “adverse effects”.

3.3.2 Study selection: inclusion and exclusion criteria

The inclusion criteria included randomized control clinical trials or controlled clinical trials, prospective and retrospective studies, published in any language, conducted on children aged 0 to 21 years with drooling which is due to cerebral palsy and other neurodevelopmental abnormality, and patients who received at least one sub serotype of BoNT-A. The studies were excluded if the

participants had age more than 21 years, or if the treatment was done with another serotype rather than BoNT-A.

3.3.3: *Data extraction and study quality assessment*

A reference management software (EndNote-20) was used to combine all results from different databases and delete duplicate articles. According to PRISMA guidelines, a two-step selection was followed: First, the two authors (HO and AM) screened independently all the titles and abstracts to make a first selection (**Figure 3.1**). In case of disagreement, the full text was read by both authors to resolve discrepancy. Secondly, the full text of all selected articles was read to extract data regarding participants, intervention, outcomes, and study design. If any data was missing from the paper, the authors were contacted for further clarification. Papers, other than English language were translated and the data was extracted. To ensure that data extraction was accurate, a third review author (SW) randomly checked 25% of extracted data and any uncertainty was resolved with mutual discussion.

3.3.4: Types of outcomes measurements

There was several outcome measures to evaluate drooling. In this manuscript, the drooling severity and frequency scale (DSFS) was used as summarised in a recent statement (**Appendix B**). In brief, this scale consider the severity of drooling, classified in a 5-level domain ranging from 1 (dry) to 5 (profuse drooling); and the frequency of drooling ranging from 1 (no drooling) to 4 (constant drooling).

3.3.5: Statical analysis

Descriptive statistics was used to summarize the data, with average and range for continuous variables and frequencies and percentages for nominal/dichotomous variables. The adverse side effects was calculated as number of events per 100 and pooled in random-effects models with MetaXL (Version 5.3). Results were considered statistically significant for a two-tailed *P* value<0.05.

3.4 Results

3.4.1 Description of studies

A total of 535 articles were identified. Following the exclusion of 158 duplication or reports unrelated to drooling and/or BoNT-A, 133 manuscripts were eligible for full text reading (**Figure 1**). An additional 112 studies were excluded, as they were either abstracts or irrelevant studies regarding pediatric population, leaving 21 studies for further full-text evaluation in the systematic review. From these, 12 studies were removed from the meta-analysis because they did not match our inclusion criteria. The reasons for inclusion and exclusion after screening are listed in the **Appendix C** Thus, the qualitative and quantitative analysis was conducted with nine clinical studies involving BoNT-A as the treatment of drooling in children (Alrefai *et al*., 2009), (Alvarenga *et al*., 2017), (Banerjee *et al*., 2006), (Bothwell *et a*l., 2002), (Gubbay & Blackmore, 2019), (Jeung *et al*., 2012), (Ong *et al*., 2009), (Sales *et al*., 2021), (Tiigimäe-Saar *et al*., 2012).

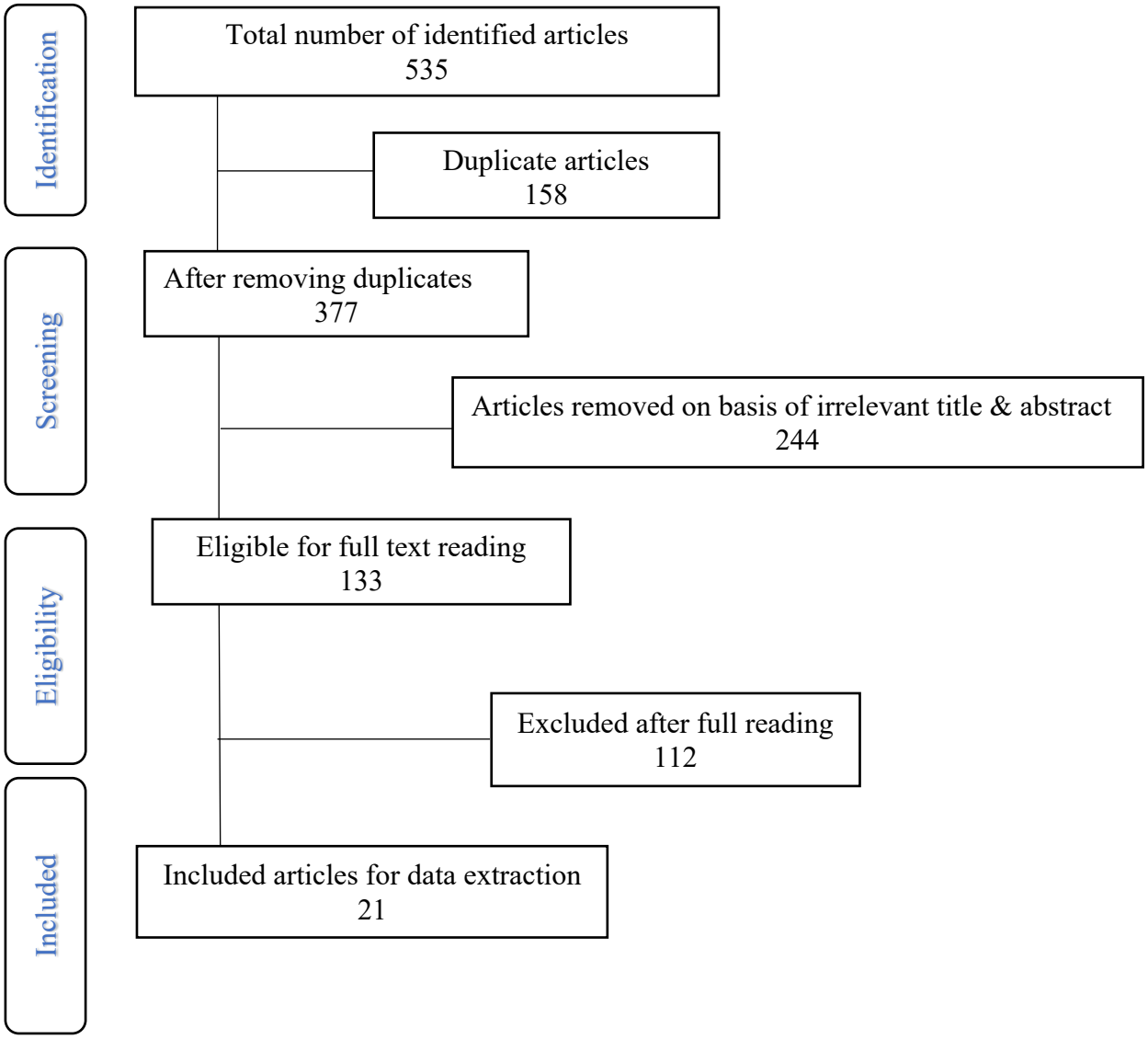


Figure 3.1: A comprehensive search was conducted in online database following the principles of Cochrane Handbook for Systemic Reviews of intervention (Cumpston *et al*., 2019), to identify papers that investigated BoNT-A for treatment of drooling in children. This systemic review screened for relevant studies published up to May-2021. The flow diagram was reproduced from Mohr, Preferred reporting items for systemic review and meta-analysis. The PRISMA statement: published by PLoS Med., 2009 (Cumpston *et al*., 2019).

3.4.2 Study participants

The clinical characteristics of the patients included in this study is presented in the **Table 3.1**. The mean age of patients was nine years and six months. There were 563 patients including 52.57% (296/563) male and 47.42% (267/563) were female. Cerebral palsy was most common diagnosed neuro-disability with 70% (394/563).

Table 3.1. Clinical characteristics of the 563 patients included in the analyzed studies.

Patient characteristics	N (%)
Mean age	9.6 years
Number of patients analyzed	563
Gender	
Male	296 (52.57)
Female	267 (47.43)
Diagnosis	
Cerebral palsy	394 (70)
Other neurodevelopmental disability	169 (30)

3.4.3 Type of intervention

The study characteristics, including first author, year of publication, journal, country, and the type of intervention detail (type of BoNT-A, dose and site of injection, type of salivary glands, pre-injection severity score of drooling, and the post-injection severity score are presented in **Table 2**. All included studies reported usage of the BoNT-A (Botox) except one that used another type of BoNT-A (Dysport) (Alrefai *et al*., 2009). Three studies mentioned the injection of BoNT-A only in the bilateral parotid gland (Alrefai *et al*., 2009), (Bothwell *et al*., 2002), (Hassin-Baer *et al*., 2005), while the majority reported injection in both bilateral parotid and bilateral submandibular

gland (Alvarenga *et al*., 2017), (Banerjee *et al*., 2006), (Formeister *et al*., 2014), (Gubbay & Blackmore, 2019), (Jeung *et al*., 2012), (Nordgarden *et al*., 2012), (Ong *et al*., 2009), (Pena *et al*., 2009), (Reid *et al*., 2013), (Sürmelioğlu *et al*., 2018), (Suskind & Tilton, 2002), (Tiigimäe-Saar *et al.*, 2012), (Wu *et al*., 2011). One study reported unilateral parotid gland and bilateral submandibular gland (Sales *et al*., 2021), while another study mentioned bilateral parotid gland and unilateral submandibular gland (Wilken *et al*., 2008). There was variation in doses of BoNT-A ranges from 60U to 100U and average dose was used as 1.1unit/kg/gland (Ong *et al*., 2009), (Pena *et al*., 2009), (Squires *et al*., 2012). Units are not interchangeable between different serotypes of BoNT-A all included studies reported usage of botox® except one (Alrefai *et al*., 2009) that mentioned use of dysport® dose range was 100-140 units. All studies reported usage of ultrasound guidance for administration of injection except one study (Alrefai *et al*., 2009). Local anesthesia, in gel or cream, was reported by 05 studies before BoNT-A injections. Six studies reported usage of general anesthesia in form of inhalation and intravascular. Four studies mentioned both (local and general anesthesia) in combination. One study reported use of IV sedation and remaining five studies did not specify any anesthesia type. For the assessment of drooling, the severity and frequency scale (DSFS) was the most used tool by 11 (52.38%) studies , while 3 (14.28%) studies reported usage of teacher drooling scale (TDS), two (9.52%) studies used visual analogue scale (VAS), two studies (9.52%) reported drooling quotient (DQ), number of bibs and drooling impact was reported by one study each and one study reported use of four tools (DSFS, DQ,VAS, No of bibs).

Table: 3.2 Interventional characteristics of the included studies using BoNT-A for the treatment of drooling in children.

Study	Patients (n)	Age Mean (range)	Site	BoNT-A	Dose Mean (range)Unit	Ultrasound guided	Anesthetic /Sedation	Tool
Alrefai *et al.* 2009[a]	24	(1.8-7)	BPG	Dysport	(100 -140)	No	NS	DSFS
Alvarenga *et al.*2017	17	(4-19)	BPG +BSMG	Botox	30	Yes	GA	DSFS
Banerjee *et al.* 2006	20	10.8 (6-16)	BPG +BSMG	Botox	50.9 (30.4- 70)	Yes	LA + GA	DSFS
Bothwell *et al.* 2002	09	4-17	BPG	Botox	5	NS	LA	DSFS
Formeister *et al.*2014	21	8.9 (0.9-18.2)	BPG+ BSMG	Botox	1.1 unit/kg/gland	Yes	NS	TDS
Gubbay 2019	15	(3-14)	BPG+ BSMG	Botox	1.1 unit/kg/gland	Yes	LA +GA	DSFS
Hassin-Baer *et al.* 2005	09	10.5 (6-18)	BPG	Botox	31.7	Yes	LA	DSFS
Jeung *et al.* 2012	17	(11.8-3.2)	BPG+ BSMG	Botox	100	Yes	NS	DSFS
Jongerius *et al.* 2004	45	(3-16)	BSMG	Botox	15	Yes	GA	TDS
Mahadevan *et al.* 2016	26	(7M-18Y)	(BSMG)	Botox	100	Yes	GA	DSFS
Nordgarden *et al.* 2012	06	13.7 (10-18)	BPG +BSMG	Botox	100	Yes	GA	DQ
Ong *et al.* 2009	21	(4-12)	BPG+ BSMG	Botox	(60-80)	Yes	IV sedation	DSFS, DQ,VAS, # OF BIBS
Pena *et al.* 2009	36	8.6 (1.4-19.8)	BPG+ BSMG	Botox	1.1 unit/kg/gland	Yes	LA +GA	# OF BIBS
Reid *et al.* 2013	26	(6-18)	BPG+ BSMG	Botox	100	Yes	GA	DI

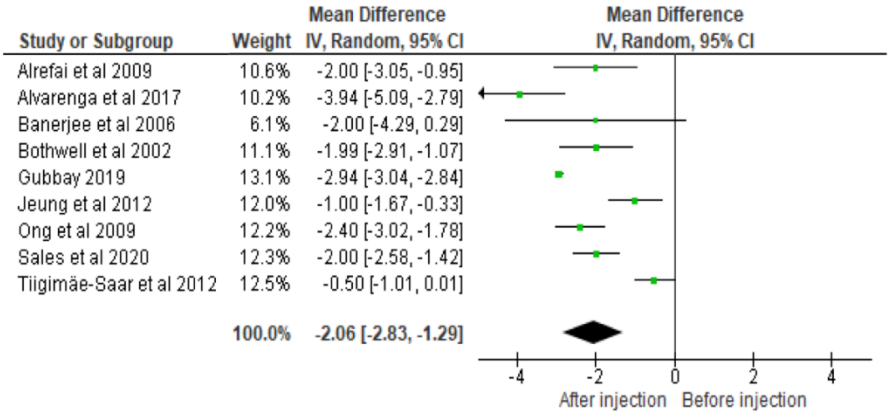
Sales *et al.* 2020	23	(2.3-3.2)	UPG+ BSMG	Botox	25	Yes	LA	DSFS
Sürmelioğlu *et al.* 2018	27	11 (6-16)	BPG +BSMG	Botox	100	NS	NS	VAS
Suskind *et al.* 2002	17	(8-21)	BPG+ BSMG	Botox	NS	Yes	LA	DQ
Tiigimäe-Saar *et al.* 2012	09	(1.6-11)	BPG+ BSMG	Botox	100	Yes	LA + GA	DSFS
Van Hulst *et al.* 2020	160	(3-17)	(BSMG)	Botox	25	Yes	GA	VAS
Wilken *et al.* 2008	15	9.8(1-18)	BPG+ USMG	Botox	(80-100)	Yes	LA	TDS
Wu *et al.* 2011	20	(3-17)	BPG+ BSMG	Botox	100	Yes	NS	DSFS

Sedation include, local anaesthesia (LA) in form of topical gel or cream, general anaesthesia (GA), nitrous oxide inhalation, intravenous. Dose of BoNT-A varies among different studies. Dose of BoNT-A injected as per unit/kg/gland or in pre-defined units from. Site of injection included, Bilateral parotid gland (BPG), bilateral submandibular gland (BSMG), unilateral submandibular gland (USMG) and unilateral parotid gland (UPG), all included studies reported use of botox except one (alrefai)[a] that reported another serotype of BoNT-A (dysport), different assessment techniques were used, drooling severity and frequency scale (DSFS), teacher drooling scale (TDS), visual analogue scale (VAS), drooling impact (DI) scale, drooling quotient (DQ) and number of bibs,in some studies data was not specifies (NS).

3.4.3 Primary outcome measurement

Drooling severity and frequency scale was used in 12 studies. Among them, nine articles had complete and sufficient data for the meta-analysis (**Figure 3.2**). It was observed that there was a significant reduction in the frequency and severity of drooling, comparing the children before and after BoNT-A injections. BoNT-A was found to significantly decrease the severity of drooling in patients with sialorrhea (standardized mean difference [SMD], −2.06; 95% confidence interval

[CI], −2.83 to −1.29; *P*<0.0001) when compared with the conditions before injections using random effects models (**Figure 3.2**).



IV= Inverse variation

Figure 3.2. Forest plot of the studies evaluating the decrease of the severity and the frequency of drooling using BoNT-A injection before and after the treatment of sialorrhea. CI = confidence interval.

3.4.4 Adverse effects

The adverse effects that occurred during and after the injection are presented in **Table 3.3**. Ten studies reported mild to moderate adverse effect. Six studies reported dysphagia (Alvarenga *et al*., 2017), (Jongerius et al., 2004), (Nordgarden *et al*., 2012), (Sales et al., 2021), (Tiigimäe-Saar *et al*., 2012), (Wilken *et al*., 2008). Two studies reported transient increase in saliva after first injection after one week (Alrefai *et al*., 2009), (Bothwell *et al*., 2002). Thickening of saliva was found in two studies (Nordgarden *et al*., 2012), (Ong et al., 2009). Dry mouth was reported by one study (Reid et al., 2013), where 17 patients out of 26 reported xerostomia (Reid *et al*., 2013). Other adverse side effects included pain and swelling at site of injection, speech difficulties, dental plaque, and flu like syndrome.

Table 3.3: Adverse side effects reported by the studies evaluating the use of BoNT-A in children with sialorrhea.

STUDY	ADVERSE EFFECT	NUMBER OF PATIENTS N (%)
Alrefai *et al.* 2009	Transient increase in drooling	2 (8.33)
Alvarenga *et al.* 2017	Mild dysphagia	1 (5.88)
Bothwell *et al.* 2002	Increase in saliva	1 (11.11)
Jongerius *et al.* 2004	Dysphagia Flu-like syndrome	5 (11.11)
Nordgarden *et al.* 2012	Dysphagia Increased dental plaque index Speech difficulties, thicker saliva	3 (50)
Ong *et al.* 2009	Pain and swelling Thick saliva with halitosis Fever Difficulty with chewing	9 (42.85)
Reid *et al.* 2013	Dry mouth	17 (65.38)
Sales *et al.* 2020	Dysphagia Dry cough	2 (8.69)
Tiigimäe-Saar *et al.* 2012	Dysphagia	1 (10)
Wilken *et al.* 2008	Dysphagia	5 (33.33)

3.5 Discussion:

In this systemic review and meta-analysis, the effectiveness of BoNT-A for the treatment of drooling in children was evaluated, and the adverse side effects were measured before and after the injections. Results from individual studies demonstrated a moderate to significant reduction in drooling in children with neurological disability after treatment with BoNT-A.

There is no worldwide consensus on a primary assessment outcome tool for drooling. Both subjective and objective metrics have been used to evaluate the adverse side effects, severity and the clinical benefits during treatment. Patients or their caregivers have filled out subjective scales

including the DRS, DSFS, VAS, and DI scale to describe their qualitative and quantitative impression of the severity and impact of the drooling (Srivanitchapoom *et al*., 2014), (Wu *et al*., 2011). However, quantification of the amount a child drools, both for intervention and for research purposes, has been difficult in developing methods of assessment that translate into valid and meaningful results in children (Rodwell *et al*., 2012). For quantitative methods involving salivary flow measurement, the counting number of bibs per day and DQ were the most used objective measures of drooling (Wilken *et al*., 2008), (Suskind & Tilton, 2002). However, the DSFS was the most frequently used outcome measure in the studies reviewed, and in many studies, it was claimed to be an accurate measure of drooling that can be used to guide therapeutic drooling treatment, especially in individuals who are unable to complete drooling quotient assessments (Rashnoo & Daniel, 2015). Considering these criteria, our meta-analysis showed a significant decrease in severity and frequency of drooling in children after BoNT-A injection. In some studies (Pena *et al*., 2009), (Ong *et al*., 2009), the number of bibs per day were counted and this outcome was considered more practical and relevant as a quantitative method by physicians, parents and caregivers involved in the everyday management of drooling (Rodwell *et al*., 2012). However, while this assessment provides an estimate of drooling quantification, it does not represent the effects of drooling on children and their families (Rodwell *et al*., 2012). According to Blasco (2002), these measures of drooling were frequently insufficient and the most crucial indicator for children and the caregivers was the change in the drooling condition (Blasco, 2002).

In term of safety, BoNT-A was found to be an effective and safe treatment for drooling in children. It was observed that a few patients had side effects after injection, but most of them had mild to moderate transient adverse events. In this systemic review, six studies reported dysphagia as common adverse effects after the first injection (Alvarenga *et al*., 2017), (Jongerius *et al*., 2004),

(Nordgarden *et al*., 2012), (Sales *et al*., 2021), (Tiigimäe-Saar *et al*., 2012), (Wilken *et al*., 2008). one study reported speech problems (Nordgarden *et al*., 2012). Saliva thickness and dental plaque were also reported in two studies (Nordgarden et al., 2012), (Ong *et al*., 2009) and this may have been associated with changes in salivary composition caused by intraglandular cholinergic blockade (Erasmus *et al*., 2010).

3.6 Conclusion

BoNT-A was found to be a clinically effective therapy that reduced drooling severity in children with sialorrhea. Although there were some adverse side effects reported, they were transient and not severe. Future studies are now needed to determine the best techniques, and to identify the ideal dosages, required to achieve optimal outcomes.

CHAPTER 4

Discussion

4.1 Overall discussion:

Botulinum neurotoxin has been known for 100 years but it has been used for medical purpose for only the last two decades. There is a lot that is not known about this neurotoxin, and its usage as a diagnostic and therapeutic agent is still in early stages. Researchers are trying to better understand its long-lasting effects, treatment plans that are most efficient, and reasons behind its failures.

BoNT is formed mainly by the anaerobic bacterium clostridium, clinically BoNT-A is most beneficial among seven serotypes of BoNT ranges from type A to G.

Hypersalivation or sialorrhea is a challenge for children with neurological and muscular disorder such cerebral palsy. Initially, anticholinergic drugs like glycopyrrolate and scopolamine were commonly used as a first line treatment for drooling. However they can be difficult to bear due to their side effects (e.g, constipation, xerostomia, urinary retention, dizziness, and other behavioural changes.)

Another option for management of drooling is surgical treatment for those who fail to respond pharmacological therapy. Surgical treatments include, salivary duct ligation, salivary duct re-routing and salivary gland excision. The risk and complications of invasive surgical treatment such as nerve injury, xerostomia and sialocele make this treatment option unacceptable to many individuals with severe neuromuscular problems.

BoNT injection of the major salivary glands has been found to reduce saliva production and improve drooling with efficacy up to 95%. This procedure has a good clinical success rate and a low complication rate when performed under ultrasound supervision. Moreover, it can be easily injected under local anaesthesia which make this procedure painless in children.

Despite its popularity among clinicians, the botox A serotype of BoNT-A has been used as an off-label drug for drooling in children and there are no worldwide acceptable guidelines available for its usage in drooling for children. In this thesis, a systemic review and meta-analysis has been presented. The review showed that different types of BoNT-A have been used for drooling in children. Botox has been used frequently by clinicians, but recently in December 2020, the FDA approved Xeomin, another type of BoNT-A, for drooling children. Dysport, the third type of BoNT-A, was found to be rarely used for drooling. It was also found that after FDA approval for Xeomin, most physicians in USA and Europe were using it as a treatment of choice for drooling in children.

4.2 Future directions:

Based on the results of this thesis, further studies are necessary to compare the three commonly used types of BoNT-A, Xeomin, Botox and Dysport. There is a need to determine if Xeomin, a pure form of BoNT-A, might be a better option of treatment in pediatric population. Further studies are needed to evaluate the best injection techniques, and to identify the ideal dosages to achieve optimal outcomes.

It is proposed that a clinical trial should be done to evaluate the clinical efficacy, and the potential side effects of different forms of BoNT-A for treatment of drooling in children. After obtaining

approval from the Ethical Review Committee of the institution, data could be collected from the sialorrhea clinic of the Lethbridge-Layton-Mackay Rehabilitation Centre, and from the Saliva Management clinic at Montreal Children's Hospital. Those patients meeting the inclusion criteria should be enroled in this study. A multidisciplinary rehabilitation facility should be used to recruit children who drool. The children would normally be evaluated by a physiotherapist, a speech therapist, and a neurologist. Drooling patients should be tested by the centre physician using a rating scale that assesses the seriousness and frequency of drooling, and those who receive a cumulative score of seven or higher should be admitted. Patients who received a Botulinum neurotoxin injection for some other purpose in the previous 6 months should be removed from the study. The research should be set up so that patients will receive 1unit/kg/gland units of Incobotulinum neurotoxin (Xeomin) and 1unit/kg/gland Onabotulinum neurotoxin (Botox) and Abobotulinum neurotoxin (Dysport) in the second visit four months later, regardless of the first injection's answer. The caregivers should sign a consent document that stating awareness of the situation. Data obtained from drooling severity and frequency (DSFS) measurement scale should be plotted using Microsoft Excel and analyzed using SPSS. The study results should be published with an assurance that in the event of a negative outcome, results will be made available, as appropriate through publication, or will be reported to the regulatory authorities.

Chapter 5

Conclusion

5.1 Summary of thesis

Chapter 1 presented an overview of the problem to be investigated and described the aim and the objectives of study. Chapter 2 discussed the associated anatomical structures and functions of salivary gland, provided a brief detail about saliva and the description of drooling including, contributing factors, classification, clinical assessment, drooling measurement techniques and management modalities. Chapter 3 presented the systemic review and meta-analysis conducted on BoNT-A. It was concluded that BoNT-A including its serotypes (Botox, Dysport) is a clinically effective therapy for drooling in children, reported adverse side effects were mild and transient. Chapter 4 provided an overall discussion, and then proposed that a clinical trial should be done to compare three most frequently used types (Xeomin, Botox, Dysport) of BoNT-A to determne their efficacy and adverse effects during treatment of drooling in children with neurological disabilities. Chapter 5 presented an overall discussion.

5.2 Overall conclusion

BoNT-A was found to be a clinically effective therapy for drooling in children. Also, reported adverse side effects were mild and transient. Further studies are required for optimal dosages and techniques of injection in children.

Appendix A

("botulinum neurotoxin" OR "Botulinum toxin A" OR "Incobotulinum" OR "Abobotulinum" OR "Onabotulinum" OR "Botox" OR "Dysport" OR "Xeomin"):ti,ab,kw AND (Sialorrhea or drooling or hypersialorrhea or polysialia or ptyalism or salivary hypersecretion or salivation or sialorrhea or sialorrhoea or sialosis):ti,ab,kw AND (newborn or neonat or infant or child or adolescent or paediatric or baby or babies or toddler or kid or kids or boy or girl or juvenile or teen or youth or pubescen* or preadolesc* or prepubesc* or preteen or tween):ti,ab,kw)

Appendix B

Drooling severity and frequency scale (DSFS) Scale

Severity:

1 = Never drools, dry

2 = Mild-drooling, only lips wet

3 = Moderate- drool reaches the lips and chin

4 = Severe- drool drips off chin & onto clothing

5 = Profuse- drooling off the body and onto objects (furniture, books)

Frequency:

1 = No drooling

2 = Occasionally drools

3 = Frequently drools

4 = Constant drooling

Appendix C

The reasons for inclusion and exclusion after screening:

Inclusion criteria*:*

1. Randomized control clinical trials
2. Controlled clinical trials,
3. prospective and retrospective studies,

   published in any language,
4. children aged 0 to 21 years
5. Patients who received at least one sub serotype of BoNT-A.

Exclusion criteria:

1. Age more than 21 years,
2. Used another serotype rather than BoNT-A
3. Unpublished studies
4. Different methodology
5. Patients who received other type of BoNT than BoNT-A

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