Treatment outcomes and complications of Intra-glandular Onabotulinum Toxin-A Injections under Electromyography-Guidance in children with sialorrhea

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Preface and Contribution of Authors

Manuscript 1: (Chapter 3: Clinical uses of Pediatric Electromyography in Otolaryngology)

Sam J. Daniel participated in the conception and design of the study and manuscript revision. Mohammed AlNoury constructed the search strategy, reviewed all related articles, and drafted the manuscript. Mariana Smith participated in manuscript drafting. All authors have participated substantially to the final manuscript and approved the final version.

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Manuscript 2: (Chapter 4: Treatment outcomes and complications of Onabotulinum Toxin-A Injections under Electromyography-Guidance in children with sialorrhea: A prospective study)

Sam J. Daniel was the project leader. He participated in the study design, performed the electromyography-guided Onabotulinum Toxin-A injections in children with sialorrhea, and revised the manuscript. Mohammed AlNoury participated in data acquisition, data analysis under supervision, and manuscript writing. All authors have participated substantially to the final manuscript and approved the final version.

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Manuscript 3: (Chapter 5: Secondary non-response of Intra-glandular Onabotulinum-Toxin A injections in a child with sialorrhea)

Sam J. Daniel performed the Onabotulinum Toxin-A injections into the salivary glands and revised the manuscript. Mohammed AlNoury participated in data collection and manuscript drafting. Isabel Cardona proofread the manuscript. All the authors have participated substantially to the final manuscript and approved the final version.

Abstract

Background:

Sialorrhea is the unintentional loss of saliva from the mouth. Onabotulinum Toxin-A (OBTXA) injections has proven beneficial for the treatment of sialorrhea. OBTXA injections can be directed either with manual palpation, ultrasound guidance, or less commonly with electromyography (EMG) guidance. EMG is used to record the electrical activity generated in the muscles, which can aid in avoiding OBTXA injections into the muscles overlying as well as deep to the salivary glands. It is postulated that this could lead to better outcomes and fewer complications. Studies on the efficacy and safety of OBTXA injections under EMG guidance for the management of sialorrhea in children are scarce.

Objectives:

The objectives of this thesis are 1) to provide an overview on the use of pediatric EMG in the field of Otolaryngology – Head & Neck Surgery; 2) to measure and monitor treatment outcomes and complications after EMG-guided OBTXA injections into the salivary glands in children with sialorrhea; and 3) to discuss the management of secondary non-response to OBTXA injections due to the production of neutralizing antibodies against OBTXA.

Materials and methods:

First, a comprehensive review of the literature was done to identify the clinical uses of pediatric EMG in the field of Otolaryngology – Head & Neck Surgery. Second, a prospective cohort study was undertaken to measure treatment outcomes and complications of EMG-guided OBTXA injections in children with sialorrhea by comparing various drooling scales at baseline and 4 months after receiving EMG-guided OBTXA injections. Complications were also documented. Third, a case report of secondary non-response to EMG-guided OBTXA injections in a child with sialorrhea is presented to demonstrate the treatment strategy for managing secondary non-response to OBTXA.

Results:

1) A total of 36 articles were reviewed. It was found that pediatric EMG can help to distinguish between vocal fold paralysis and fixation in children. It can also predict the prognosis and recovery of vocal fold paralysis and facial nerve paralysis. Moreover, it can be used to monitor the facial and recurrent laryngeal nerves intra-operatively in various types of head and neck surgeries. EMG also aided in guiding BTX/OBTXA injections in children with sialorrhea, with adductor laryngeal breathing dystonia, and with essential palatal myoclonus.

2) Of the 26 children who received EMG-guided OBTXA injections, there was significant reduction of sialorrhea in all subjective and objective measurement scales ($p \leq 0.05$), with improvement in the child's and family's social lives, and in the child's physical health, but this did not reach statistical significance. There were no complications after EMG-guided OBTXA injections.

3) One limitation for the use of OBTXA injections is secondary non-response due to the formation of neutralizing antibodies against OBTXA. This was observed in a 12- year-old child who improved after receiving EMG-guided OBTXA injections and then developed resistance 2 years after receiving OBTXA treatment. Increasing the OBTXA dose did not resolve the issue. After cessation of the injections for 1 year, injections were resumed and the patient began to show improvement, without further evidence of resistance.

Conclusion:

EMG has various clinical uses in pediatric otolaryngology, including management of sialorrhea. Results demonstrated that sialorrhea was significantly reduced in children who received EMG-guided OBTXA injections, without complications. This study provides preliminary evidence for the efficacy and safety of EMG-guided OBTXA injections in children with sialorrhea. However, the frequent and long-term use of OBTXA injections may lead to the formation of neutralizing antibodies and secondary non-response to OBTXA. As demonstrated in the case study, cessation of OBTXA injections for 1 year may be helpful in resuming the efficacy of OBTXA.

Résumé

Contexte :

La sialorrhée signifie la perte involontaire de salive. L'Onabotulinum toxine A (OBTXA) a été démontrée efficace comme traitement. Les injections d'OBTXA peuvent être orientées par la palpation manuelle, par guidage échographique ou par guidage électromyographique (EMG). L'EMG est utilisée pour enregistrer l'activité électrique des muscles et peut contribuer à éviter d'injecter les muscles adjacents aux glandes salivaires. Il y a peu d'études sur l'efficacité et l'innocuité des injections d'OBTXA avec guidage EMG dans le but de gérer la sialorrhée chez les enfants.

Objectifs :

Les objectifs de cette thèse consistent à : 1) présenter un survol de l'utilisation de l'EMG en otorhinolaryngologie (ORL) pédiatrique; 2) mesurer et surveiller les résultats et les complications à la suite d'un traitement par injections d'OBTXA avec guidage EMG dans les glandes salivaires chez les enfants souffrant de sialorrhée; et 3) aborder la façon de gérer l'absence de réaction secondaire aux injections d'OBTXA en raison de la production d'anticorps qui neutralisent l'OBTXA.

Méthodologie :

Un examen approfondi de la littérature sur les utilisations cliniques de l'EMG en ORL pédiatrique a été effectué. Aussi l'étude d'une cohorte a permis d'évaluer les résultats et les complications à la suite d'injections d'OBTXA avec guidage EMG chez les enfants avec sialorrhée comparant leur état de base et celui 4 mois post-traitements. Enfin, on présente une étude de cas concernant l'absence de réactions secondaires aux injections d'OBTXA afin de démontrer la stratégie de traitement visant à gérer cette absence de réactions secondaires.

Résultats :

1) Les 36 articles retenus révèlent que l'EMG pédiatrique peut aider à faire la distinction entre la paralysie des cordes vocales et la fixation. Elle permet également de fournir un pronostic suite à une paralysie des cordes vocales ou des nerfs faciaux. De plus, on peut l'utiliser afin de surveiller les nerfs faciaux et les nerfs laryngés récurrents lors des différents types de chirurgies de la tête et du cou. L'EMG a également facilité le guidage des injections de OBTXA chez les enfants avec sialorrhée, la dystonie laryngée respiratoire des muscles adducteurs et la myoclonie palatale essentielle.

2) Sur les 26 enfants qui ont reçu des injections d'OBTXA avec guidage EMG, on a constaté une baisse considérable de la sialorrhée sur toutes les échelles de mesure subjectives et objectives ($p \leq 0,05$), de même qu'une amélioration de la vie sociale des enfants et des familles, ainsi que de la santé physique des enfants, mais cette amélioration était négligeable sur le plan statistique. Les injections d'OBTXA avec guidage EMG n'ont entraîné aucune complication.

3) Une des limites du recours aux injections d'OBTXA concerne l'absence de réactions secondaires attribuable à la formation d'anticorps qui neutralisent l'OBTXA. On fait état du cas d'un enfant dont l'état s'est amélioré après qu'il a reçu des injections d'OBTXA avec guidage EMG mais qui a ensuite développé une résistance 2 ans après. Une stratégie d’arrêt temporarire du traitement a été efficace pour gérer cette condition.

Conclusion :

L'EMG présente des applications cliniques variées en ORL pédiatrique, y compris la gestion de la sialorrhée. La sialorrhée s'est grandement améliorée chez les enfants qui ont reçu des injections d'OBTXA avec guidage EMG, sans complications. Cette étude apporte une preuve préliminaire de l'efficacité et de la sécurité des injections d'OBTXA avec guidage EMG chez les enfants aux prises avec la sialorrhée. Cependant, l'utilisation fréquente et prolongée des injections d'OBTXA peut entraîner la formation d'anticorps neutralisants et l'absence de réactions secondaires à l'OBTXA. L'interruption temporaire des injections peut contribuer à rétablir l'efficacité de cette toxine.

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Abbreviations

ALS	Amyotrophic lateral sclerosis
ALBD	Adductor laryngeal breathing dystonia
BTX/OBTXA	Botulinum Toxin/Onabotulinum Toxin-A
BVFI	Bilateral vocal fold immobility disorders
CP	Cerebral palsy
CMAP	Compound muscle action potential
CT	Cricothyroid muscle
DSFS	Drooling severity and frequency scale
DQ	Drool quotient
EMG	Electromyography
FN	Facial nerve
FP	Facial paralysis
FNS	Facial nerve stimulation
IONM	Intraoperative neuro-monitoring
L-EMG	Laryngeal electromyogram
LM	Lymphatic malformation
LD	Laryngeal dystonia

MUAP	Motor unit action potential
PCA	Posterior cricoarytenoid muscle
QOL	Quality of life questionnaire
RLN	Recurrent laryngeal nerve
SMAS	Superficial muscular aponeurotic system
SD	Standard deviation
TDS	Teacher's drooling scale
TA	Thyroarytenoid muscle
VFI	Vocal fold immobility disorders
VAS	Visual analogue scale

Chapter 1: Introduction

1.1 Study rationale and purpose

Sialorrhea (drooling) is the excessive production of saliva from the mouth [1]. One of the effective treatment options used is the injections of Botulinum Toxin/Onabotulinum Toxin-A (BTX/OBTXA) into the salivary glands [2]. It has been recommended to inject BTX under guidance to ensure better treatment outcomes and fewer complications [3-5]. One of the guidance techniques is using ultrasound, which has resulted in good outcomes [2, 6]. However, ultrasound use has a few disadvantages. One of these disadvantages is that the use of ultrasound is operator-dependent. Therefore, an experienced radiologist has to be involved, which could be challenging to find in certain centers. Another disadvantage of using ultrasound is the difficulty in holding and placing the ultrasound probe on top of the glands while a child is active and agitated, leading to inaccurate visualization of the needle inside the glands. For this reason, many children undergo general anesthesia, which carries known risks, in order to perform what is essentially a relatively non-invasive procedure.

Another way to guide BTX injections is the use of electromyography (EMG). This approach has many advantages, including the fact that it is not operator-dependent and that there is no need for general anesthesia. Unfortunately, only a few studies have reported on the use of EMG-guided BTX injections into the salivary glands. Also, the EMG technique used in this project has not been used in children before. The need to evaluate the effectiveness in children of EMG-guided BTX injections formed the rationale of this thesis.

1.1.1 The concept and purpose of using EMG to direct Botulinum Toxin/Onabotulinum Toxin-A injections into salivary glands

The purpose of this thesis is to evaluate the effectiveness of EMG-guided BTX/OBTXA injections in the management of sialorrhea in children. In order to understand how EMG would improve treatment outcomes, we need to understand the relations of the muscles overlying and deep to the parotid and submandibular glands.

A) *Parotid gland*

The parotid gland overlies the lateral boarder of the masseter muscle [7] (Fig. 1.1 and 1.2). The superficial muscular aponeurotic system (SMAS), a cutaneous muscular system lying within the layers of the superficial fascia of the face, is attached to the parotid sheath that covers the parotid gland [8] (Fig. 1.3). If BTX/OBTXA injections were given superficially into the SMAS, it could lead to minimal treatment outcomes and if they were given deep into the masseter muscle, it would lead to less effective outcomes and chewing difficulties. Thus, we believe that using EMG would confirm the placement of the needle inside the parotid gland, avoiding the SMAS and the masseter muscle, resulting in better outcomes and the absence of complications (Fig. 1.4).

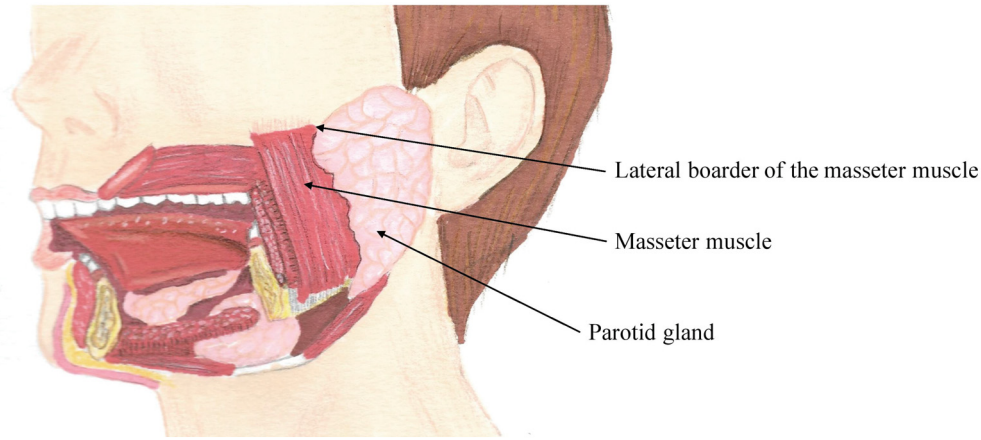

Fig. 1.1 The parotid gland overlies the lateral boarder of the masseter muscle.

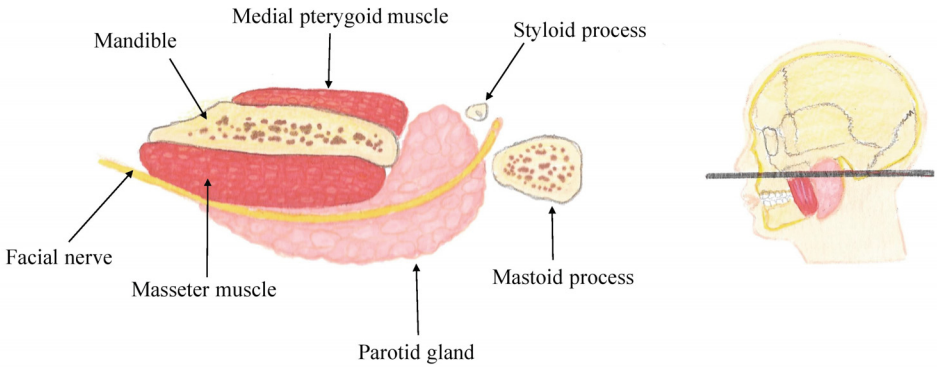

Fig. 1.2 A transverse cut section showing the deep relation of the masseter muscle to the parotid gland.

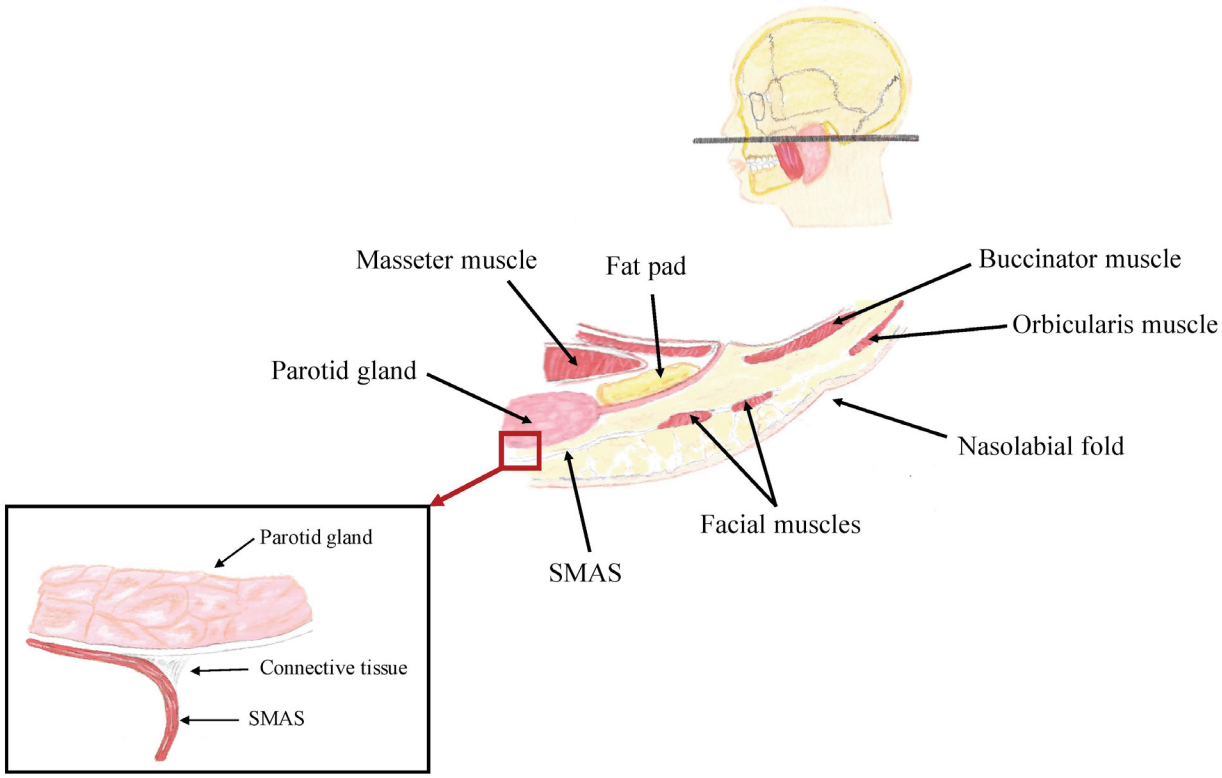

Fig. 1.3 A transverse cut section showing the superficial relation of the superficial muscular-aponeurotic system (SMAS) and the deep relation of the masseter muscle to the parotid gland. © McGill Auditory Sciences Laboratory 2016

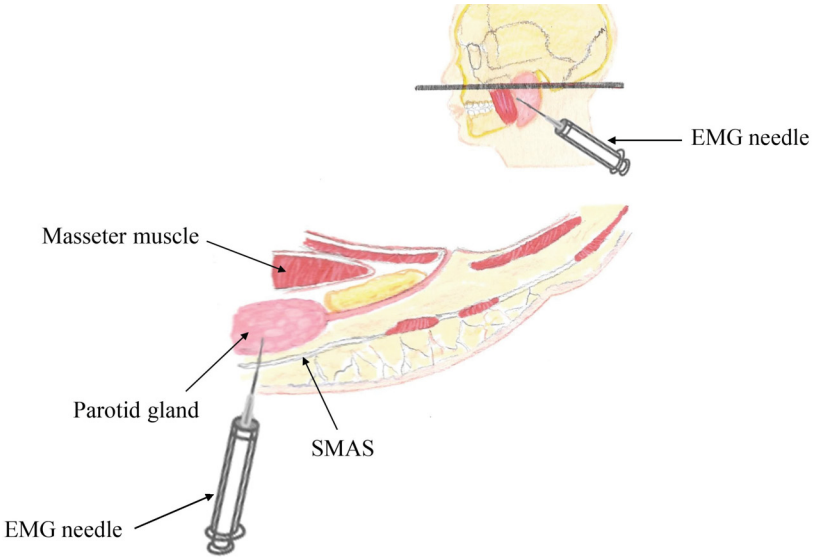

Fig. 1.4 A transverse cut section showing the placement of the Electromyography (EMG) needle inside the parotid gland avoiding superficial muscular aponeurotic system (SMAS) and the masseter muscle. © McGill Auditory Sciences Laboratory 2016

B) Submandibular gland

The submandibular gland is located in the submandibular triangle, posterolateral to the mylohyoid muscle. It is bounded superiorly by the edge of the mandible and inferiorly by the anterior and posterior bellies of digastric muscle (Fig. 1.5 and 1.6). It is also covered by the skin and the platysma muscle [9-11] (Fig. 1.7). We believe that using EMG-guided BTX/OBTXA injections will confirm the placement of the needle inside the submandibular gland and avoid injections superficially into the platysma muscle and deep into the mylohyoid, digastric, and hypoglossus muscles (Fig. 1.6, 1.7, and 1.8). Thus, leading to better outcomes and no complications.

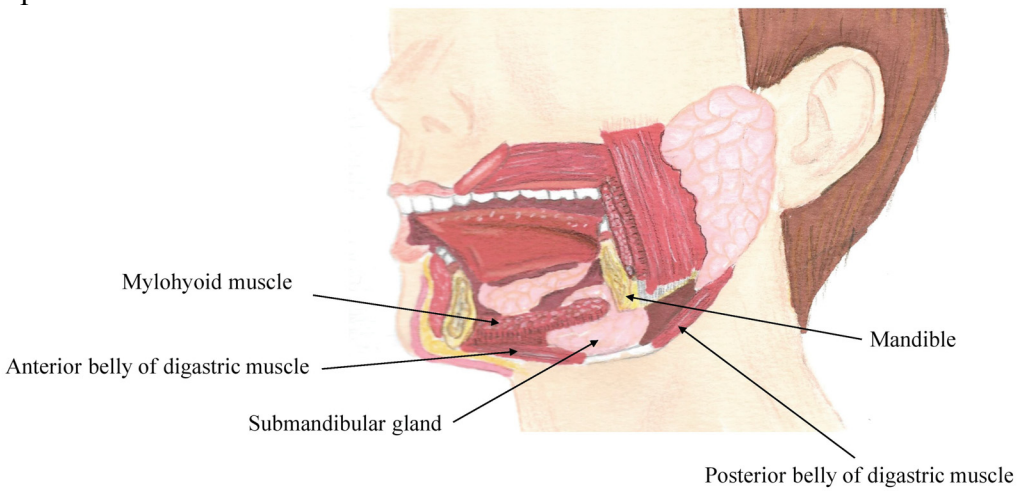

Fig. 1.5 The submandibular gland lies below the mandible and its deeply related to the mylohyoid and digastric muscles. © McGill Auditory Sciences Laboratory 2016

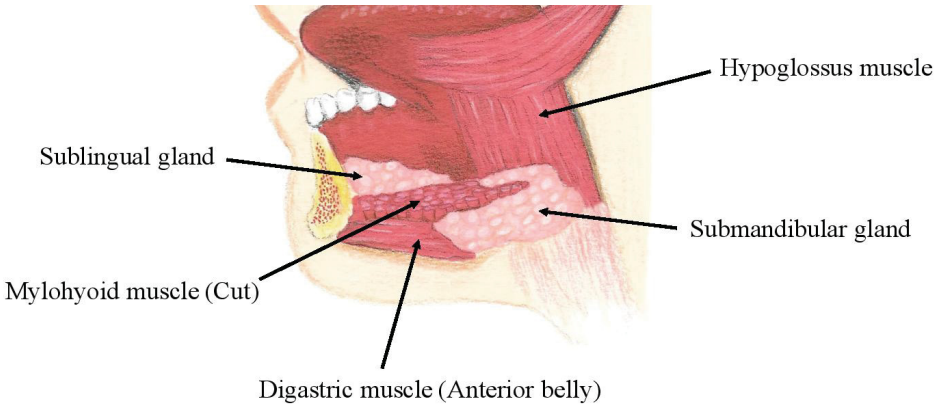

Fig. 1.6 A sagittal section showing the deep muscles related to the submandibular gland (mylohyoid, digastric, and hypoglossus muscles). © McGill Auditory Sciences Laboratory 2016

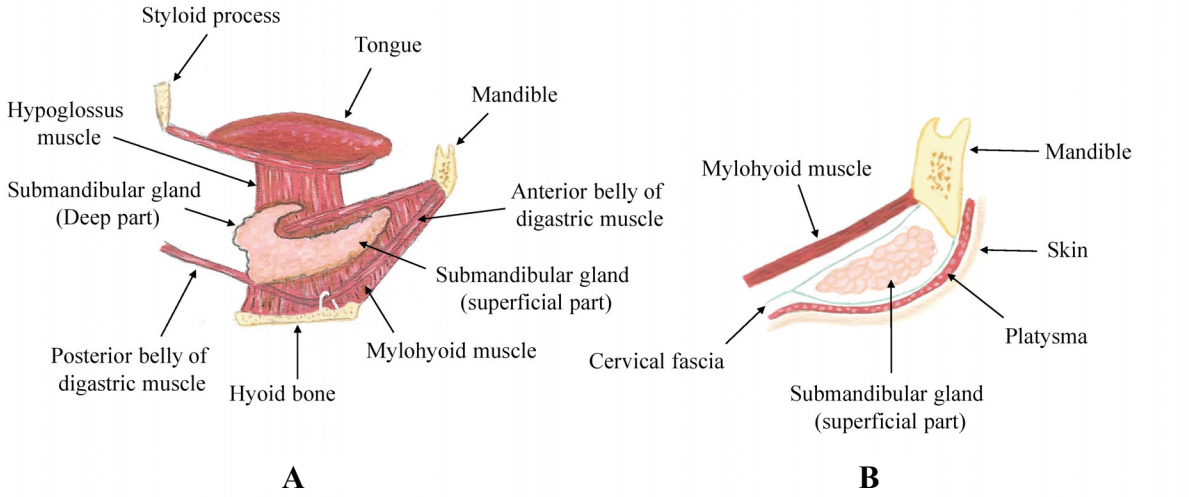

Fig. 1.7 A) A sagittal section showing the muscles related deep to the submandibular gland (Mylohyoid, anterior and posterior bellies of digastric, and hypoglossus muscles).

B) A coronal section showing the superficial relation of skin and platysma muscle to the submandibular gland.

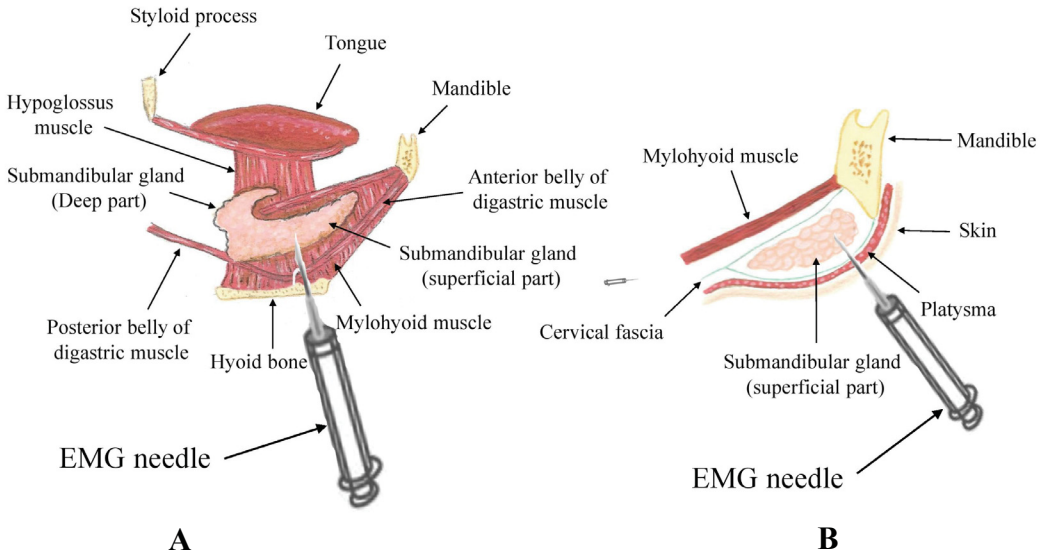

Fig. 1.8 A) A sagittal section showing the placement of Electromyography (EMG) needle inside the submandibular gland avoiding deep injections into the mylohyoid, digastric, and hypoglossus muscles.

B) A coronal section showing the placement of EMG needle inside the submandibular gland avoiding injecting superficially into the skin and the platysma muscle.

1.2 Objectives

The objectives of this thesis are: 1) to provide an overview on the use of pediatric EMG in the field of Otolaryngology – Head & Neck Surgery, 2) to measure and monitor treatment outcomes and complications after EMG-guided OBTXA injections into the salivary glands of children with sialorrhea, and 3) to discuss the management of secondary non-response to OBTXA injections due to the production of neutralizing antibodies against OBTXA.

1.3 Thesis structure

This thesis is in a manuscript-based format. In chapter 2, sialorrhea and recent clinical-care treatment options are overviewed. In chapter 3, the various clinical uses of pediatric EMG in the field of otolaryngology are reviewed. In chapter 4, the results of a prospective cohort study that measures treatment outcomes and complications after EMG-guided OBTXA injections in children with sialorrhea are reported. In chapter 5, the case of a child with sialorrhea is described, who initially improved after receiving OBTXA injections under EMG guidance but then developed resistance against OBTXA to discuss the treatment strategy. This case illustrates one of the limitations of OBTXA injections when treating sialorrhea. In chapter 6, the thesis findings, clinical and research implications, and overall conclusion are presented.

Chapter 2: Literature review of sialorrhea and treatment options

2.0 Introduction

This chapter provides a general overview on the definition, pathophysiology, and treatment options for sialorrhea, especially BTX injections into the salivary glands.

2.1 Salivary glands

The salivary glands are exocrine glands, which are divided into major and minor salivary glands. The major salivary glands include the parotid, submandibular, and sublingual glands [12]. Of these, the parotid gland is the largest. It is located in the pre-auricular region, and is divided by the facial nerve into superficial and deep lobes [13]. The submandibular gland is the second largest salivary gland located in the submandibular triangle and lies posterolateral to the mylohyoid muscle. The smallest of the salivary glands is the sublingual gland, which is situated in the anterior floor of the mouth [12, 13] (Fig 2.1).

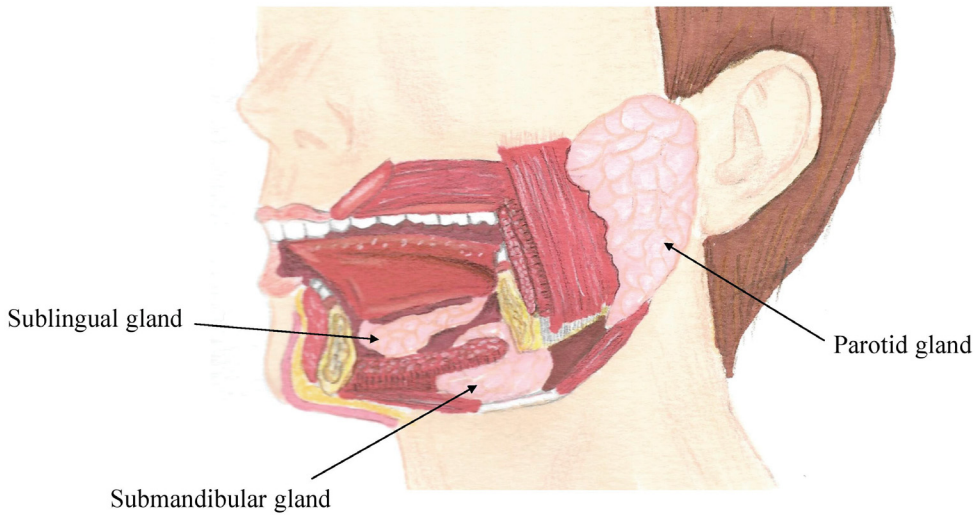

Fig. 2.1 Major salivary glands. © McGill Auditory Sciences Laboratory 2016

2.2 Saliva physiology and production

Saliva is secreted by the salivary glands under the control of the sympathetic and parasympathetic autonomic nervous system. Saliva has a major role in lubrication, digestion, immunity, and maintenance of human body homeostasis [12]. The submandibular glands secrete 70% of the saliva in the unstimulated resting state; the parotid glands secrete most of the saliva in the stimulated state, such as while chewing. During the stimulated state, saliva is secreted in much larger amounts, i.e., five times greater than in the resting state [14].

2.3 Sialorrhea

Sialorrhea, also known as drooling, is the excess amount of saliva in the mouth with saliva flowing beyond the lip margin [1]. Sialorrhea is considered abnormal after the age of 4 [15]. It can be either due to increased production of saliva or, most commonly, due to decreased saliva clearance [16].

Sialorrhea can be an isolated phenomenon caused by hypersalivation, or it may occur in conjunction with neurological disorders such as Parkinsonism and amyotrophic lateral sclerosis (ALS), or as a side-effect of medication. Most often, it is due to chronic neurological disorders that cause a disturbance in the oral, palatal, and lingual musculature leading to pooling of saliva from the mouth [17]. In children, the most common cause is cerebral palsy (CP), with an incidence of sialorrhea of 10–38% in CP children [15-17].

Sialorrhea can be classified into anterior or posterior drooling. Anterior drooling is saliva that spills from the mouth, whereas posterior drooling is saliva spilled through the faucial isthmus, increasing the risk of saliva aspiration [18, 19]. There are several factors that can contribute to sialorrhea and these include inadequate lip closure, open-mouth posture, limited tongue movement, poor oropharyngeal coordination during swallowing, malocclusion, dental caries, and flexed posture [18-22]. Sialorrhea can lead to complications, such as skin maceration and irritation, dental caries, halitosis, and aspiration pneumonia [18, 19, 23, 24]. Moreover, sialorrhea can cause psychosocial complications, such as social isolation, impaired interaction

with family and peers, and overburden of care on family/caregiver(s) [25, 26]. All these complications can negatively affect the quality of life of the child, and of the child's family.

2.4 Evaluation of sialorrhea

Sialorrhea varies in frequency (infrequent, occasional, frequent, or constant) and severity (mild, moderate, severe, or profuse). Although, there are no reliable and valid measurement tools for evaluating sialorrhea, various tools have been used in an attempt to assess the condition. These tools can be classified into either subjective or objective measurement scales [27].

Several subjective scales have been used to evaluate drooling outcomes, which rely on an observer's impression of the quantity of drooling. These scales include the Drooling Severity and Frequency Scale (DSFS) [28] (Table 2.1), the Teacher's Drooling Scale (TDS) [29] (Table 2.2), the Visual Analogue Scale (VAS) [2], and the Drooling Impact Scale[30]. The most common subjective scales used in the literature are DSFS and TDS. Another way to measure drooling is with a Quality of Life questionnaires (QOL), which subjectively measures the impact of drooling on the daily quality of life [6, 23, 25, 31-33].

Several objective measurement tools have been used in patients with sialorrhea. For example, counts of the number of bibs/clothes/towels changes per day [27]; measurement of saliva volume during cannulation of the salivary duct [6], measurement of saliva weight using dental rolls [27, 32], the Drooling Quotient (DQ) [34], and measurement of saliva flow rate [6, 27, 35]. Cannulation of the salivary duct is considered to be the gold standard for drooling measurement, but it is difficult to carry out in children [6]. Measuring the impact of different treatment methods can be done by placing dental rolls inside the mouth and measuring the weight of the roll before and after sialorrhea treatment. This is one of the most widely used objective measurements [32]. However, there are several difficulties that arise when using this method: It may trigger a gagging reflex or attempts to swallow the cotton by children [6]. The DQ, described by Reddihough, is a count of the number of times that drool is absent or present, beyond the lip margin, measured at a 15-seconds intervals over a 10-minute period (40 observations in 10-min) [34] or over a 5-minute period, as proposed by Van Hulst et al. [36].

DQ is a costly and time-consuming method, and the data are insufficient to confirm its validity and reliability [36].

The most commonly used validated drooling scales:

Table 2.1 Drooling Severity and Frequency Scale (DSFS)[28]
Drooling severity scale
1 = Never drools, dry
2 = Mild – drooling, only lips wet
3 = Moderate – drool reaches the lips and chin
4 = Severe – drool drips off chin and onto clothing
5 = Profuse – drooling off the body and onto objects
Drooling frequency scale
1 = No drooling
2 = Occasional drools
3 = Frequently drools
4 = Constant drooling

Table 2.2 Teacher's Drooling Scale (TDS)[29]
1 = No drooling
2 = Infrequent drooling; small amount
3 = Occasional drooling; intermittent all day
4 = Frequent drooling; but not profuse
5 = Constant drooling; always wet

2.5 Treatment options for sialorrhea

Treatment options for managing sialorrhea can be either conservative or invasive. Conservative treatments include oral behavioral therapy, intra-oral devices, such as palatal training devices, and medications, such as anticholinergic drugs [35, 37-40]. Invasive approaches include surgery, such as salivary duct ligation/rerouting or salivary glands excision, or radiation [39]. Recently, BTX injections into the salivary glands have been shown to be an effective treatment method to manage sialorrhea in both children and adults [41-45]. Other studies have advocated a multidisciplinary approach to managing sialorrhea, including the contribution from an otolaryngologist, a pediatrician, an occupational therapist, a speech and language pathologist, a dentist, a neurologist, and a social worker [46].

2.5.1 Medications

Medications used to manage sialorrhea typically include anticholinergic agents, such as glycopyrrolate, benztropine, scopolamine, and tropicamide [38, 40, 47, 48]. Anticholinergic medications exert their effect by down-regulating acetylcholine, which leads to decreased saliva secretion through the parasympathetic nervous system [39]. Glycopyrrolate oral solution is the first drug which has been approved in the United States for drooling in children with chronic neurological disorders [1]. However, its use is limited due to increased saliva thickness, which can be troublesome for children with chronic neurological disorders, as they often have associated dysphagia. Medications can be taken orally, or they can be applied transdermally, such as with transdermal scopolamine [49, 50]. However, many side effects can arise from using anticholinergic medications, which may result in the discontinuation of the drugs. These side effects include constipation, urinary urgency and retention, confusion, blurred vision, and hypotension [51-53].

2.5.2 Surgery

Several surgical procedures are invasive measures that are used as a last resort for when trying to manage sialorrhea. Such procedures include salivary gland excision, denervation of the salivary glands, and transposition or ligation of the salivary ducts [39, 44, 51, 54].

Because such surgeries are invasive and a permanent treatment option, such treatments should be reserved for only the most severe and intractable cases.

2.5.3 Radiation

Radiotherapy has also been used to manage sialorrhea, as acinar cells are sensitive to ionizing radiation. However, its use is controversial, as it can be carcinogenic and it may cause side effects such as mucositis and osteoradionecrosis. Therefore, radiotherapy as a treatment for sialorrhea is not recommended in children [39, 55].

2.5.4 Botulinum toxin injections

BTX is a potent neurotoxin that blocks the release of acetylcholine from the synaptic vesicles in the post-ganglionic parasympathetic fibers, leading to reduction of saliva secretion [56]. The effect of BTX on sialorrhea was first noted in patients with Parkinson disease [4]. Several clinical trials, retrospective studies, and case studies have shown the effectiveness of BTX in managing sialorrhea in children [2, 6, 33, 35, 52, 57-61]. A recent meta-analysis study, which included all randomized placebo controlled trials, concluded that BTX significantly decreased sialorrhea severity in both the adult and pediatric populations [62]. Moreover, the overall efficacy rates of BTX had a range of 47% to 83% [63], while others reported higher rates of 89% [64] and 95% [65]. The advantages of using BTX injections for treating sialorrhea include limited side effects, low risk of aspiration, convenience, and reduced invasiveness compared to surgery [62]. However, increased costs, the requirement for repeated injections (every 4–6 months), and the possibility of developing antibodies against BTX are some of the reported limitations of using BTX injections for managing sialorrhea [18, 41, 57, 62].

BTX is usually injected into the parotid and/or the submandibular glands, as they are the greatest contributors to saliva production [57]. There is a controversy in terms of what gland should be injected: either the submandibular glands only [35, 58, 66], the parotid glands only [5, 59, 60], or both [61, 64]. Some authors advocate the use of general anesthesia when injecting BTX into the salivary glands in the pediatric population [32, 33, 44, 61, 63], while others use local analgesia [6, 35, 45, 60]. There are 7 different serotypes of BTX, of which type A and B are

the most commonly used [51]. The dose of BTX used in different studies has varied, but the recommended dose is weight-dependent, with an average of 1.4 U/kg in each parotid gland, and 0.6 U/kg in each submandibular gland [44, 57, 67].

BTX injections can be guided either with anatomical landmarks, or by ultrasound guidance [5, 68]. When using anatomical landmarks to inject the parotid glands, injections are directed into two sites, (a) behind the angle of the ascending mandibular ramus and (b) into the infero-posterior portion of the gland, just before the mastoid process [68] (Fig. 2.2). The submandibular gland injections can be performed at two sites under the maxillary arch in the submandibular triangle [69] (Fig. 2.2). The use of ultrasound-guided BTX injections have been supported by many studies that had the aim of avoiding unintended diffusion of BTX into the surrounding muscles in order to obtain better treatment outcomes and fewer complications [2, 3, 6, 58, 67, 70]. In one adult study on 15 patients with Parkinsonism, who underwent either ultrasound-guided BTX injections (n = 8) or anatomically-guided injections (n = 7), there was a significant reduction in sialorrhea in the group of patients who received ultrasound-guided injections after 1 week [3]. Another study showed a subjective improvement of 66.7% when injecting BTX without guidance and they concluded that the degree of saliva reduction as related to the accuracy of BTX injections within the salivary glands [4].

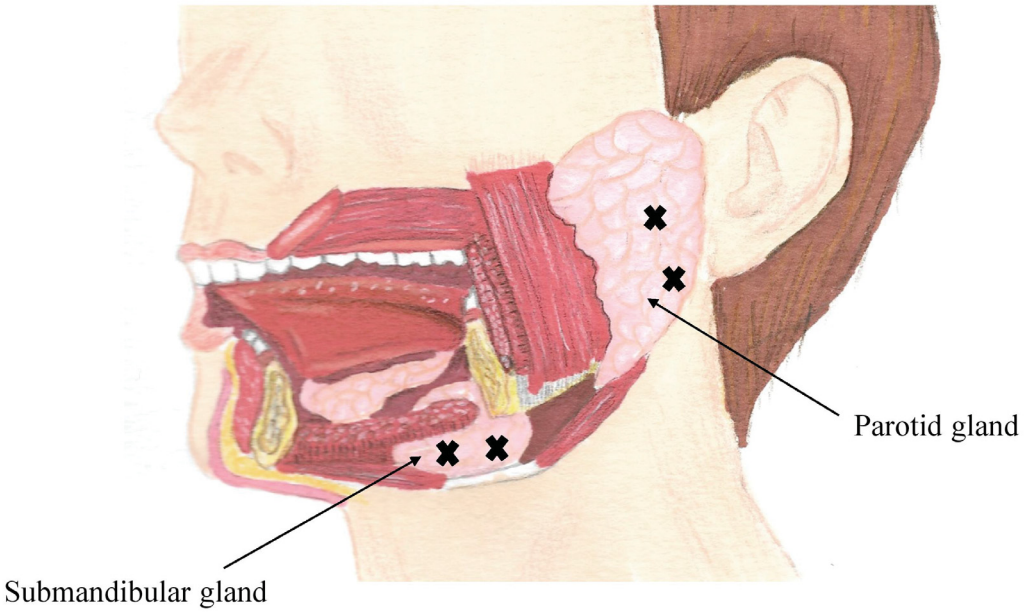

Fig. 2.2 Sites of Botulinum Toxin injections into the parotid and submandibular glands using anatomical-landmarks (✖).© McGill Auditory Sciences Laboratory 2016

Another way of guiding BTX injections is to use electromyography (EMG). EMG guidance has been shown to be effective in directing BTX injections into the desired muscle group in patients with neuromuscular disorders, leading to maximum treatment effect [71]. Extending this idea, EMG usage should help confirmation of the placement of the needle inside the salivary glands by indicating when the needle was not within the overlying muscles over the glands. Thus, this suggests that EMG usage should produce better outcomes and fewer complications. Jackson et al. used EMG to guide BTX injections into the salivary glands in 20 ALS patients with sialorrhea [69]. They confirmed the placement of the needle inside the glands by the absence of the motor unit action potential (MUAP). Using this method, they showed significant reduction in sialorrhea with fewer adverse events [69]. Studies on the use of EMG-guided BTX injections into the salivary glands in children are scarce. Daniel et al. reported a significant improvement of sialorrhea in a case series of three children with familial dysautonomia, who received EMG-guided BTX injections into the parotid glands [45]. Pena et al. used EMG needle to stimulate the facial muscles while injecting BTX to avoid facial nerve injury [72]. They described their approach as follows: "After placing the needle, electrical stimulation was initiated to visualize facial muscle twitching. If twitching occurred, the needle was repositioned to avoid facial nerve injury". Another study by Savarese et al. used an EMG guidance to direct BTX injections into the parotid glands [67]. There was a significant reduction in sialorrhea, as assessed using both subjective (visual analogue scale) and objective (number of bibs used per day) scales.

2.6 Complications after Botulinum Toxin injections into the salivary glands

Complications of BTX injections were classified into minor or major based on outcomes by the Society of Interventional Radiology (Table 2.3) [73]. According to this classification, minor complication rates reported ranged from 0% [6, 55] to 11% [35] after injecting the submandibular glands, and from 0% [33, 64] to 18% [74] after injecting both submandibular and parotid glands. Major complications rates ranged from 0% [6, 33, 64, 72] to 7% [74] after injecting the submandibular and parotid glands. These complications include increased saliva thickness (3.9%), dysphagia (3.3%), pneumonia (2.2%), and dry mouth (3.3%) [57, 62]. Other studies reported reversible parotitis due to the reduced amount of saliva [75]. Another possible complication is injury to the facial nerve, but this has not been reported in children [60].

Table 2.3 The society of Interventional Radiology classification system based on outcomes [73]
Minor Complications
A. No therapy, no consequence.
B. Nominal therapy, no consequence; includes overnight admission for observation only.
Major Complications
C. Require therapy, minor hospitalization (<48 hours)
D. Require major therapy, unplanned increase in level of care, prolonged hospitalization (>48 hours)
E. Permanent adverse sequelae
F. Death

2.7 Linking statement

Chapter 2 indicates that BTX injections have been shown to be effective in managing sialorrhea. Many studies have recommended the use of ultrasound or EMG guidance for better outcomes. However, there have been no reports in the literature with regards to the different clinical uses of EMG in children in the field of otolaryngology. Thus, the following manuscript will present a review of the use of EMG in pediatrics in Otolaryngology—Head and Neck Surgery, particularly in guiding BTX injections into the salivary glands in children with sialorrhea. This is the first manuscript that overviews the various clinical uses of pediatric EMG in Otolaryngology.

Chapter 3: Clinical uses of Electromyography in Pediatric Otolaryngology

(Manuscript 1)

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Keywords**:** children, electromyography, otolaryngology, head and neck, sialorrhea.

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3.1 Abstract:

Electromyography (EMG) is used to record electrical activity generated in the muscles. There are various applications of EMG in the field of otolaryngology. However, there is scarce description of its use in children. The purpose of this narrative comprehensive review is to highlight the clinical uses of pediatric EMG in the field of otolaryngology. Pubmed (NLM), Medline (OvidSP), Embase (OvidSP), Cochrane (Wiley), Biosis (OvidSP), AMED (OvidSP), Global Health (OvidSP), and Web of Science (Thomson Reuters) databases were searched to retrieve articles by using the following terms: "electromyography", "head and neck", "otolaryngology", and "children" in various combinations. A total of 36 articles were eligible for inclusion. Our review revealed that EMG can help to 1) distinguish between vocal fold paralysis and vocal fold fixation in children and to predict recovery of vocal fold immobility disorders; 2) predict prognosis and guide treatment strategies in children with facial nerve paralysis; 3) provide intraoperative monitoring of the facial and recurrent laryngeal nerves; and 4) guide BTX injections to manage sialorrhea, adductor laryngeal breathing dystonia, and essential palatal myoclonus.

3.2 Introduction:

Electromyography (EMG) has been used as a tool that helps to detect neuromuscular abnormalities by measuring muscle responses at rest and when the patient is contracting their muscle. In general, EMG can help to establish the site of neural disease; it can also distinguish between neurogenic and myopathic muscle weakness. Moreover, it helps to detect abnormalities, such as denervation and fasciculation, and provides pathophysiological information on peripheral neuropathy, such as axonal degeneration or demyelination [76, 77].

EMG detects the motor unit action potential (MUAP), which is the summation of all innervated fibers of a given motor unit, from the muscles under study by placement of skin surface electrodes, or, more commonly, a needle and fine wire electrodes. There are various parameters of the MUAP, such as the size, shape, and stability, which provides information regarding the peripheral nervous system, i.e. the nerve, neuromuscular junction, and muscle. EMG and nerve conduction parameters change in pathological conditions, aiding in diagnosis and prediction of prognosis of various neuromuscular diseases. Moreover, special patterns, such as those indicating denervation and re-innervation, can also help in diagnosis, prognosis, and planning proper treatment [78].

The clinical scope of EMG application has greatly expanded since the work of Faaborg–Andersen and Buchtal in the late 1950's [79, 80]. However, EMG has not been used as widely in children as in adults, due to technical difficulties, poor tolerance, and the need for a skilled examiner [81, 82]. EMG has been used in various conditions related to otolaryngology, but there have been few studies on children. Therefore, the purpose of this comprehensive review is to highlight the clinical utilization of pediatric EMG in the field of otolaryngology.

3.3 Methodology:

3.3.1 Sources of data and search strategy:

A comprehensive literature search was conducted in Pubmed (NLM), Medline (OvidSP), Embase (OvidSP), Cochrane (Wiley), Biosis (OvidSP), AMED (OvidSP), Global Health (OvidSP), and Web of Science (Thomson Reuters) databeses. The literature was searched from the inception of the databases until August 15, 2016. The search retrieved articles using controlled vocabulary terms (MeSH) and variations of text words found in the title/abstract for the following terms: Electromyography (EMG), head and neck, otolaryngology, and children. The MeSH term for "Electromyography" was exploded and used in combination with the following text words: "electromyograph* or electro-myograph* or EMG" or "electr* adjacent to myograph*". This set was combined with "Head" or "Neck", both of which used exploded MeSH terms and text words for the "Head" or "Neck" and was also combined with "otolaryng* or oto-laryng* or laryng*or otology* or otorhinolaryng or oto-rhinolaryng or audiolog* or ENT or ear nose adjacent to throat". Finally, the set was limited by the MeSH for the following terms "pediatrics" or "adolescent" or "child" or "infant" or "parents" and text words for "newborn* or new-born* or neonat* or neo-nat* or infan* or child* or adolesc* or paediatr* or pediatr* or bab* or toddler* or kid or kids or boy* or girl* or juvenile* or teen* or youth* or pubescen* or parent* or mother* or father* or mom* or dad*".

3.3.2 Study selection

Initially, the first author (M.A) performed a complete screening of the articles' titles, abstracts, and keywords. Then, the first two authors reviewed the full text to report the different clinical uses of pediatric EMG in conditions related to otolaryngology–head and neck surgery. The literature search identified a total of 12470 studies, after duplicate removal. Thirty-six studies were chosen to write this review based on the following criteria: studies were reported in English, involved children fully or partially, used EMG, and were related to Otolaryngology–Head and Neck Surgery (Fig. 3.1).

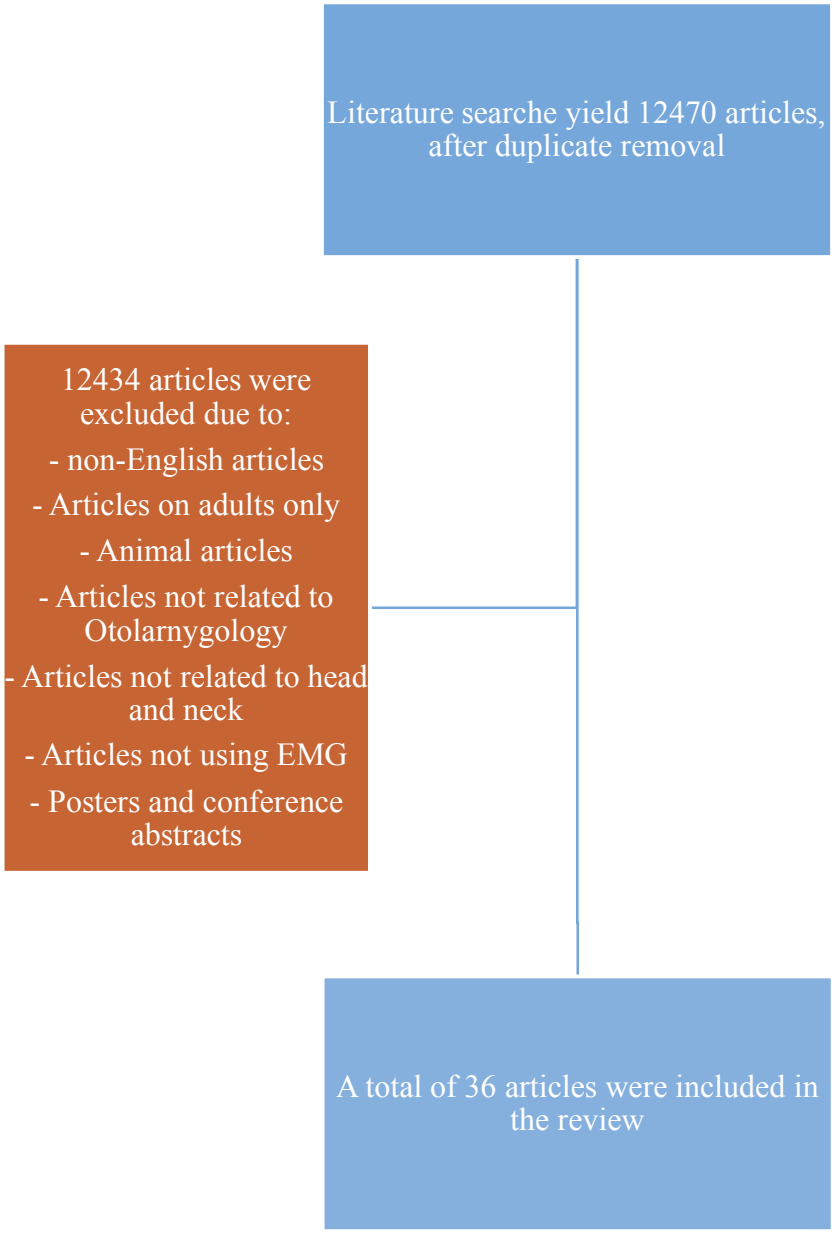

Fig. 3.1 Article review flow diagram

3.4 Pediatric EMG clinical uses in Otolaryngology:

3.4.1 Vocal fold immobility disorders:

Laryngeal EMG (L-EMG) has been widely used in adults, after being introduced in 1944 by Weddel et al., to help otolaryngologists in the diagnosis and prognosis of vocal fold immobility disorders (VFI) [77, 83-85]. However, the applications and the recommendations for the use of L-EMG in children have not been well established, particularly since this technique requires needle introduction, hindering its utilization in the pediatric population [86]. In 1987, Koch et al. were the first to report the use of L-EMG in the pediatric population by using a monopolar electrode endoscopically placed under general anesthesia in 12 children [87]. The authors concluded that L-EMG was valuable in evaluating vocal fold function in pediatric patients. Later, other authors reported successful experiences with pediatric L-EMG by using bipolar hooked wire electrodes placed transcutaneously, or concentric needle electrodes placed endoscopically into the posterior cricoarytenoid (PCA) and thyroarytenoid (TA) muscles [88, 89]. Another study used the combined approach of direct laryngoscopy under general insufflation anesthesia with spontaneous ventilation and the application of EMG with monopolar electrode placement [90]. L-EMG provides data on the activity of laryngeal muscles with detection of denervation and re-innervation patterns [86]. Therefore, this can help in (1) the differential diagnosis of VFI, (2) determining the level of the neural injury, and (3) predicting prognosis and recovery.

L-EMG is helpful to distinguish VFI caused by neuropathy and that caused by cricoarytenoid joint dysfunction in children. If L-EMG detects a denervation pattern, neuropathy is the cause of the VFI, while in cricoarytenoid joint dysfunction, the L-EMG is normal [86, 89, 91, 92]. Several adult studies have shown that the sensitivity of L-EMG in detecting VFI ranged from 33% to 100 % and its specificity ranged from 12% to 50% [84]. A study by Ysunza et al. on 25 children with unilateral VFI, matched by age and sex to 25 healthy individuals with symmetrical mobility of vocal fold found that L-EMG efficiently detected denervation, with 100% sensitivity and 92% specificity [86]. They also showed normal EMG findings in cases with cricoarytenoid joint dislocation. In another study of children with arthrogryposis, a rare congenital non-progressive joint contracture, L-EMG was shown to be effective in identifying

cricoarytenoid joint dysfunction [92]. However, Berkowitz used L-EMG on four children with idiopathic congenital bilateral VFI, and found normal L-EMG results, indicating laryngeal adductor and abductor muscle action imbalance, rather than true paralysis. Therefore, he concluded that L-EMG cannot be used to differentiate between idiopathic congenital bilateral VFI and mechanical fixation [89].

L-EMG can determine the level of neural injury by studying different laryngeal muscle responses; most commonly studied are the TA, innervated by the recurrent laryngeal nerve, and the cricothyroid (CT), innervated by the external branch of the superior laryngeal nerve. If L-EMG detects denervation patterns only from the TA, the level of the neural lesion is below the branching of the superior laryngeal nerve, affecting the recurrent laryngeal nerve, whereas if the denervation pattern is detected from the CT, the superior laryngeal nerve is the cause. If both muscles are affected, the injury is located above the level of emergence of the superior laryngeal nerve[86, 93].

Furthermore, recognizing re-innervation patterns in laryngeal muscles can be useful for monitoring recovery, predicting prognosis and planning a proper treatment strategy [86, 91]. Maturo et al. studied MUAP in children with unilateral VFI. They found that if L-EMG showed no normal MUAP of the laryngeal muscles by 6 months, it is unlikely that vocal cord function will recover. They also reported the recovery of vocal function in a child who had a normal MUAP 3 months after patent ductus arteriosus ligation [94]. Overall, L-EMG can predict the outcome of vocal fold function in children with unilateral VFI, irrespective of the cause [94, 95]. The sensitivity of L-EMG for predicting vocal fold recovery ranges from 13% to 100% and specificity for detecting poor recovery ranges between 20 to 100% [84].

3.4.1.1 Decannulation

Another potential clinical use of L-EMG is to guide the decision regarding decannulation in patients with tracheostomy. Berkowitz et al. used L-EMG, studying the TA and the PCA muscles in synchrony with intercostal EMG to study the activity of the laryngeal abductor and adductor muscles in relation to respiratory phase [96]. As PCA is the sole abductor of the larynx, it is active during inspiration; while the TA, which has an adduction action, is active during the

post-inspiration phase. If L-EMG shows normal patterns of TA and PCA activity in correlation with respiration, this indicates a positive prognostic feature and can guide tracheostomy decannulation in children with congenital bilateral VFI. AlQudehy et al. proposed a grading system using L-EMG to determine the amplitude of MUAP and the timing to the respiratory cycle. They concluded that their novel L-EMG grading was accurate (86.36%) and correlated with the requirement for tracheostomy in children with laryngeal mobility disorders [97].

3.4.2 Facial nerve dysfunction

3.4.2.1 Facial nerve paralysis

EMG can be performed to investigate facial paralysis (FP) by applying surface electrodes on four muscles innervated by the facial nerve (frontalis, orbicularis oculi, orbicularis oris, and platysma) or by applying bipolar electrodes with the anode placed between the ramus of the mandible and the mastoid and cathode in front the tragus of the ear [98-100]. EMG has limited use in identifying the cause of the FP, as it depends on a thorough history and clinical examination. However, Jaradeh, Hatanaka, and Sano reported the use of EMG in identifying the cause of FP in children with Mobius syndrome, which is characterized by congenital bilateral facial palsy and abducens nerve palsy. Their EMG results showed reduced or absent facial compound muscle action potential (CMAP) amplitude, indicating the involvement of facial motor nuclei [101-103].

The main use of EMG in FP is to predict prognosis by determining the degree of nerve damage and axonal degeneration [100]. The presence or the return of MUAP and re-innervation patterns after an initial loss are considered to be prognostic signs, suggesting that some clinical improvement would be expected within 6–12 weeks after the appearance of the re-innervation potentials [104-107]. Daniclides et al. studied the use of evoked EMG, which measures the electrical impulse of the muscle with supra-maximal nerve stimulation, on 30 children with Bell's palsy. They found that measuring the amplitude of the CMAP in the paralyzed side in comparison to the normal side could predict functional recovery. If the amplitude varied between 51% and 95% from the normal side, the neuronal damage was predicted to be minimal and functional recovery would be expected. If the muscle response was between 25% and 50%,

almost half of the children still had a complete recovery. If the response was between 11% and 24%, none of the patients had complete nerve recovery. Another way of predicting recovery is by measuring the number of axons that have degenerated. Eschapasse et al. reported an 88% agreement between a favorable electrical prognosis and a good outcome and 61% agreement between an unfavorable electrical prognosis and a bad outcome [108].

The timing of EMG use in FP varies according to whether the paralysis is acquired, or is congenital. In patients with acquired facial paralysis, EMG should be performed at 2–3 weeks after complete FP is established [109]. A recently published Clinical Practice Guideline for management of Bell's palsy made a recommendation against using EMG in patients with incomplete Bell's palsy [109]. EMG can be repeated after 2–3 weeks to compare the results to help predict a nerve's functional recovery. In congenital FP, EMG should be used as soon as paralysis is detected [107, 109].

Furthermore, EMG can help in planning surgery, suggesting either surgery before massive axonal degeneration, or avoidance of surgery in cases where surgery would not be indicated. In a study of 79 patients, both adult and children with different etiologies of facial paralysis, the treatment plan was directed according to EMG findings. For patients with good prognosis (when a great number of axons were blocked and had not yet degenerated) patients underwent medical treatment (corticosteroids, vasodilators, and physiotherapy). However, for patients with poor prognosis, (when great number of axons had degenerated), surgery was performed to ensure total decompression [108].

3.4.2.2 Facial nerve stimulation

Facial nerve stimulation (FNS) is considered one of the complications of cochlear implantation with incidence ranging between 1% and 3% [110-112]. FNS can result in significant discomfort, suboptimal use of cochlear implant, and often requires significant time spent in reprogramming. It is usually assessed by visual detection of facial movements or facial twitching, and it is difficult for children to report such movements subjectively. Hence, EMG has been used for an objective assessment of FNS. Cushing et al. used surface EMG to evaluate facial nerve stimulation objectively by using surface EMG applied on four areas (frontalis,

orbicularis oculi, orbicularis oris, and platysma). They showed a higher incidence of FNS, ranging from 31% to 78%, when using EMG than with visual detection and self-reporting [98]. Therefore, it has been recommended to use EMG to identify clinical and subclinical FNS to ensure safe and comfortable use of cochlear implants.

3.4.3 Intraoperative neuromonitoring:

Intraoperative neuromonitoring (IONM) is one of the most commonly frequently used EMG applications in the Otolaryngology–head and neck surgery field. Its purpose is to identify and assess the function of vulnerable nerves during surgery [113]. It is advisable to use IONM to avoid nerve injury and to prevent complications post-surgery in any procedure where head and neck nerves have a potential risk of damage.

3.4.3.1 Recurrent laryngeal nerve monitoring

The recurrent laryngeal nerve (RLN) can be injured during several cervical surgeries, with most published reports referring to thyroid surgery. In fact, one of the most feared complications of thyroid surgery is the injury to the RLN, which can lead to significant postoperative morbidity. Hence, it has been advocated that the identification of the RLN during thyroidectomy would help to minimize the risk of injuries [114, 115]. The use of EMG for intraoperative monitoring of the RLN can aid identification of the nerve, to help in the dissection of the RLN during difficult surgeries, and to provide postoperative prognostic information on the RLN. Intraoperative monitoring of the RLN during thyroid surgery has been used widely in adult patients, but less frequently in children [114-120].

RLN can be monitored by inserting a bipolar electrode directly through the cricothyroid membrane into the thyroarytenoid (TA) muscle. This technique was used by Brauckhoff et al. on 97 children, who underwent thyroid procedures, with and without intraoperative nerve monitoring. They found that, in the group who did not have IONM, the rate of temporary paresis was 4.55% and that of permanent paralysis was 2.27%. For the group who had IONM, the rate of temporary paresis was 1.8%, while none had any permanent paralysis [119]. Another study by Meyer et al. on 11 children undergoing thyroid surgical procedures with needle electrode

monitoring of the RLN and the external branch of the superior laryngeal nerve, reported transient paresis of only one RLN (9%) [120]. Another technique for monitoring the RLN is by using an endotracheal tube having surface electrodes, allowing documentation of both passive and evoked EMG signals of the TA muscle during surgery. In one retrospective study on five children, who underwent different head and neck surgeries, endotracheal tube monitoring was used to detect EMG activities of the laryngeal muscles. The authors concluded that this technique was adequate for IONM - as none of the patients developed permanent paralysis and 0.36% had temporary paresis when using this technique [116]. Endotracheal monitoring is simple, non-invasive, and easy to use. The principal disadvantage is related to the size of the tubes that need to be used if the outer diameter is bigger than the regular endotracheal tube. Another option for intraoperative monitoring of the RLN in young children is the use of an electrode pad designed for extraluminal post-cricoid placement, or surface electrodes applied to cuffed endotracheal tubes. However, the latter option has not been fully evaluated [116].

3.4.3.2 Facial nerve monitoring

The facial nerve (FN) is vulnerable to injury in the middle ear and mastoid surgeries, parotid surgery, and head and neck masses resection. During middle ear and mastoid surgeries, the (FN) is vulnerable to injury because of its proximity to the stapes, the oval window, the cochlea, and the vestibule [121]. Therefore, IONM of the FN has been used in such surgeries, but its routine use remains controversial [122]. The American Academy of Otolaryngology–Head and Neck Surgery states in a policy statement that performing IONM of the FN is effective, and that it minimizes the risk of iatrogenic injury [123]. There are few published studies on the use of IONM in the middle ear and mastoid surgeries [122, 124-126]. Noss et al. used IONM of the FN on a total of 262 cases, including 125 children, who underwent middle ear and mastoid ear surgeries. They described the FN as being “electrophysiologically dehiscent” when the stimulation threshold of the FN was less than 1 voltage, and thus the risk of FN injury was increased. In their series, they reported a 62% incidence of electrophysiological dehiscence in comparison with 13% dehiscence observed by the surgeon alone. Therefore, EMG will provide a greater margin of safety for preserving the FN during surgical dissection in the middle ear and mastoid surgeries [125].

EMG has also been used during FN surgical decompression, to avoid FN injury during surgical manipulation. In a prospective study on 10 patients with traumatic FN paralysis due to temporal bone fracture, with age ranges from 6 to 42 years, Ashram and colleagues found that the ability of the nerve to respond to stimulation and the ability of the EMG to record CMAP both proximally and distally to the injury site could be considered a good prognostic sign; in such cases, no further repair would be required and that satisfactory postoperative FN outcome would be expected. If CMAP was not recorded either proximally or distally, this indicated total degeneration of the fibers, which is considered to be a poor prognostic sign; in such cases, excision of the traumatized segment and end-to-end anastomoses could be considered. Furthermore, they found that patients showing mechanically elicited EMG activity during decompression of the FN had a good recovery and thus this is considered an additional sign predicting a favorable outcome [127].

Moreover, it has been advocated that the FN should be monitored during parotid gland surgery, as well as in head and neck mass resections in cases of cervicofacial lymphatic malformation (LM) and in excisions of first branchial cysts [128, 129]. In one retrospective study that included seven patients (four of them children) who underwent resection of cervicofacial LM, the authors concluded that preoperative FN mapping with continuous IONM helped to identify the FN, guide dissection, and reduce the incidence of FN paralysis [128]. Isaacson et al. studied the use of continuous intraoperative EMG monitoring of the FN during excision of first branchial cleft cysts in 11 children [129]. They found that EMG was able to identify the FN trunk, by employing low current (0.1–0.25 mA) stimulation. Moreover, they advised usage of this technique with simple cysts that are not infected or previously operated, emphasizing that EMG might report false results of FN location, and that anatomical identification is strongly recommended under these circumstances [129].

3.4.4 EMG to guide Botulinum Toxin injections:

EMG has been used to guide botulinum toxin (Botox; BTX) injections during the management of various disorders in pediatric otolaryngology, particularly in children with sialorrhea, laryngeal dystonia, and palatal myoclonus.

3.4.4.1 Sialorrhea:

Sialorrhea is the excessive pouring of saliva from the mouth due to either increased saliva production or, more commonly, decreased saliva clearance [130]. Children with chronic neurological disorders, such as cerebral palsy (CP), suffer from sialorrhea due to a lack of oral motor control. BTX injections into the salivary glands have been shown to be an effective treatment option for sialorrhea in children [41-43, 46]. BTX inhibits the release of acetylcholine in the cholinergic nerve ending, leading to decreased salivation [56]. EMG has been used to properly guide BTX injections into the salivary glands. The purpose of EMG use is to avoid injection of BTX into the muscle, leading to better outcomes, with fewer complications. Jackson et al. used EMG to guide BTX injections into the salivary glands of 20 amyotrophic lateral sclerosis (ALS) patients with sialorrhea. They confirmed the placement of the injection needle inside the glands when the MUAP was absent. They reported a significant reduction in sialorrhea with few adverse events [69]. However, there are few studies on the use of EMG-guided BTX injections into the salivary glands in children. Daniel et al. reported a significant improvement in sialorrhea in a case series of three children with familial dysautonomia, who received EMG-guided BTX injections into the parotid glands [45]. In another retrospective study on 36 children with sialorrhea, EMG has been used to inject BTX into the parotid glands. This study used an EMG needle to initiate an electrical stimulation, with the observation of facial muscle twitching. If twitching occurred, the needle would be repositioned away from the FN. They reported significant reduction in saliva production without complications [72]. Another prospective study on 19 children showed a reduction of drooling without side-effects after receiving BTX injection under EMG guidance into the parotid glands [67].

3.4.4.2 Laryngeal dystonia:

Laryngeal dystonia (LD), also known as spasmodic dysphonia, is an idiopathic focal dystonia that results in irregular contraction of the laryngeal muscle during phonation or during respiration. It is most commonly found in adults. It can be classified as and adductor (most commonly), abductor, or mixed LD [131]. BTX was shown to be effective in management of adult adductor LD by injection into the TA and lateral CA muscles, and managing abductor LD by injection into the PCA muscle [131-134]. EMG can be used to guide BTX injections into the

laryngeal muscles and can confirm placement of the EMG needle within the laryngeal muscles by showing distinct MUAP during phonation [135-137].

Another type of LD is called adductor laryngeal breathing dystonia (ALBD). ALBD is a rare dystonia that presents as adduction of the vocal cords during inspiration [138]. ALBD is different from adductor LD; adductor LD is task-specific, and occurs only during speaking and not during breathing. Studies on children with LD are scarce, due to the rarity of the disease in the pediatric population. There has been a report of a 10-year-old boy with ALBD who presented with severe inspiratory stridor [139]. The patient was managed successfully by injecting BTX into the TA muscles under EMG guidance.

3.4.4.3 Palatal myoclonus:

Essential palatal myoclonus (EPM) is a rare disease that is associated with involuntary repetitive contractions of the soft palate. It has been described in adults, but rarely in children. Different etiologies have been suggested, including stroke, brain stem lesions, olivary hypertrophy, or other congenital malformations of the brain. The main symptom is an objective clicking tinnitus due to a unilateral and bilateral opening of the Eustachian tube caused by contractions of the musculus tensor veli palatine [140, 141]. [140, 141]. BTX treatments have been used successfully to manage EPM [142, 143]. EMG can help to detect the involuntary muscle contractions, as reported by Jamieson et al. [144]. Moreover, it can guide injections into the muscles exhibiting the maximal myoclonic activity. One retrospective study on 10 patients, three of whom were children aged between 6 and 10 years, EPM was managed successfully by BTX injections under EMG guidance [145]. Krause et al. described a case of a 10-year-old girl with palatal myoclonus who was successfully treated with BTX injections into the tensor veli palatine muscle and remained symptom-free for 18 months [146]. Another 12-year-old case of EPM, remained free of tinnitus, 1 week after receiving BTX injections under EMG guidance [147].

3.5 Conclusion:

EMG has various clinical applications in children, which are useful for pediatric otolaryngologists. It can help to distinguish between vocal fold paralysis and vocal fold fixation. It can also help to predict recovery of vocal fold immobility disorders. EMG can be used in children with facial nerve paralysis to predict prognosis and to guide treatment strategies more optimally. Moreover, EMG has been used for intraoperative monitoring of the facial and recurrent laryngeal nerves in different surgical procedures. Furthermore, BTX injections under EMG guidance have been shown to be effective in managing sialorrhea, adductor laryngeal breathing dystonia, and essential palatal myoclonus (Fig. 3.2).

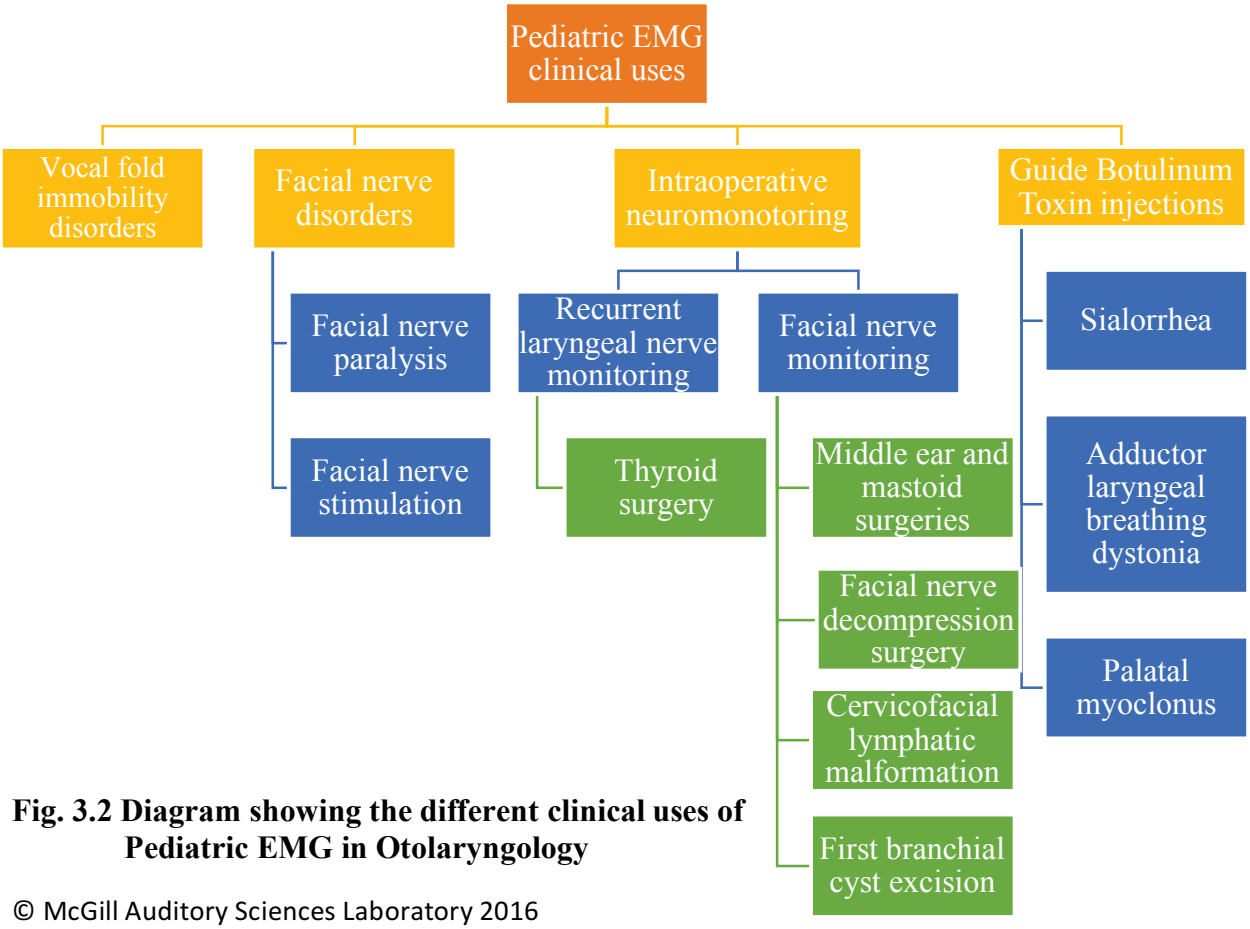

Fig. 3.2 Diagram showing the different clinical uses of Pediatric EMG in Otolaryngology

3.6 Linking statement:

EMG has various clinical implications for children in the field of otolaryngology, as reviewed above. One of these implications is that usage of EMG-guided BTX injections into the salivary glands should be useful for the management of sialorrhea in children. The next chapter presents a prospective study aimed at measuring treatment outcomes and complications associated with EMG-guided BTX injections in children with sialorrhea.

Chapter 4: Treatment outcomes and complications of Onabotulinum Toxin-A Injections under Electromyography-Guidance in children with sialorrhea: A prospective study

(Manuscript 2)

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Keywords: Sialorrhea, Drooling, Onabotulinum toxin-A, electromyogram (EMG), pediatrics.

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4.1 Abstract

Background: Onabotulinum toxin A (OBTXA) injection is a treatment option for sialorrhea. OBTXA injections can be directed either with manual palpation, ultrasound guidance, or less commonly, using electromyography (EMG) guidance. Studies on the efficacy and safety of OBTXA injections under EMG guidance for the management of sialorrhea in children are scarce.

Aim: To describe treatment outcomes and complications after EMG-guided OBTXA injections into salivary glands in children with sialorrhea.

Methods: A prospective cohort study was carried out at the Saliva Management Clinic at MAB-Mackay Rehabilitation Centre. Children with a medical diagnosis of sialorrhea who were eligible for receiving OBTXA injections were enrolled. EMG was used to guide the injections into the parotid and submandibular glands. Each child had two visits, one at baseline and one at 4 months after the injections. Pre- and post-injections, a self-administered drooling questionnaire, comprising 13 questions, using a five-point rating scale, was used to assess treatment outcomes. These scales are divided into subjective scales, objective scales, the impact of drooling on the child's social life, and the impact of drooling on the child's physical health. Subjective scales included drooling frequency and severity scales, while objective scales included scales on the need to change bibs/clothes due to drooling, the number of bibs/clothes changes per day, and the frequency of mouth wiping per day. The impact of drooling on social life was assessed by considering the impact of drooling on the child's social life, its effect on the family and on the community, and its effect on child's activity outside home. Scales assessing the impact of drooling on physical health included questions on skin irritation of the face and neck, episodes of choking/aspiration, noisy breathing, and halitosis. Additional scales were created to ascertain family satisfaction and their desire to continue with treatment. Post-injection complications were also reported. Statistical analyses were performed using descriptive statistics for all variables and paired *t*-tests to compare the 13 drooling questionnaire items pre- and post-injections. P-values $\leq$ 0.05 were considered to indicate statistical significance.

Results: Twenty-six children were enrolled in this study. Half were male (50%) with a mean age of 8.7 years ± 4 (SD) and the average length of post-injections follow-up was 4.15 months ± 0.6 month. There was a significant difference in the mean scores of drooling frequency (3.58 ± 1.06; P = 0.0001) and severity (3.08 ± 0.97; P = 0.001) after EMG-guided OBTXA injections as compared to the baseline mean scores (4.4 ± 0.85 and 3.54 ± 0.98, respectively). For objective measurements, mean scores at baseline for scales on the need to change bibs/clothes due to drooling, number of bibs/clothes changes per day, and the frequency of mouth wipes per day were 2.96 ± 1.6, 2.58 ± 1.6, and 3.69 ± 1.19, respectively. After EMG-guided OBTXA injections, these mean scores were 2.65 ± 1.38, 2.08 ± 1.59, and 3.04 ± 1.39, respectively, which showed significant improvement over the baseline mean scores (P = 0.05, P = 0.004, and P = 0.007, respectively). Mean scores assessing the child's social life, effect on the family, effect on the community, and effect on activity outside the home at baseline were 2.4 ± 0.9, 2.5 ± 1.1, 3 ± 1.3, and 2.7 ± 1.2, respectively. A slight but non-significant improvement was observed after EMG-guided OBTXA injections on both scales for the impact of drooling on the child's social life and the effect on drooling on the family (2.2 ± 1; P = 0.23, and 2.3 ± 0.8; P = 0.52, respectively). In contrast, marked improvement was observed in scales for the effect of drooling on the community and on activity outside the home after EMG-guided injections (2 ± 1.2; P = 0.0001 and 2.3 ± 1.2; P = 0.01, respectively). Results for scores on the effect of drooling on physical health were similar at baseline and after EMG-guided injections (all P > 0.05). No post-injection complications were observed.

Conclusion: This study showed that EMG-guided OBTXA injections were associated with significantly decreased drooling in both subjective and objective drooling scales, with no incidence of complications after EMG-guided OBTXA injections.

4.2 Introduction:

Sialorrhea is the unintentional loss of saliva from the mouth [51]. It is a disorder commonly seen in patients with neurological diseases due to lack of oral motor function and dysphagia, rather than the excessive production of saliva [62, 148-150]. For example, the prevalence of sialorrhea in children with cerebral palsy was reported to be 58%, with 33% suffering from severe sialorrhea requiring treatment [151]. Although sialorrhea is not a life-threatening condition, it causes several medical complications, such as irritated facial skin, oral and perioral infections, halitosis, dehydration and more seriously, aspiration pneumonia. Additionally, chronic sialorrhea can negatively impact the quality of life of both the children and their families [25, 32, 150, 152].

A number of therapeutic options are available for the management of sialorrhea, including oral motor therapy, behavioral management, systemic anticholinergic medications, radiation therapy, and surgery [52, 55, 153]. Recently, Onabotulinum Toxin-A (OBTXA) injections into the salivary glands have been shown to be an effective and non-invasive treatment option for the management of sialorrhea in both adults and children [2, 4, 6, 33, 35, 58, 64]. OBTXA can be injected into the parotid and submandibular salivary glands by manual palpation or under ultrasound guidance [154, 155]. Recently, electromyography (EMG) has been successfully used to direct OBTXA injections into the desired muscle groups in both adult and pediatric populations having various neuromuscular disorders [71, 156, 157]. The purpose of using this guidance technique when injecting the salivary glands was to avoid injection into the muscles overlying and deep to the glands, which can lead to therapy failure and side-effects [45, 69]. However, the efficacy and complications of OBTXA injections under EMG guidance for the management of sialorrhea in children have never been systematically studied.

The objectives of the current study were to measure treatment outcomes and complications after EMG-guided OBTXA injections into salivary glands in children with sialorrhea.

4.3 Material and Methods:

4.3.1 Study design and setting

A prospective cohort of patients referred to our saliva management clinic. This study received ethical approval from McGill University Institutional Review Board.

4.3.2 Population

The study population was children with a medical diagnosis of sialorrhea who were eligible for receiving treatment with intra-glandular OBTXA injections. The inclusion criteria consisted of: (i) age less than 18 years; (ii) a diagnosis of moderate to severe sialorrhea, and (iii) no OBTXA injections in the past 6 months. Children who had received anticholinergic medication or who had underwent salivary glands surgery were excluded.

4.3.3 Data collection

A prospectively collected database included age, gender, medical diagnoses, medications taken, and date of previous OBTXA injections. A self-administered drooling questionnaire was used to measure baseline levels of various drooling grading scales.

At the follow-up visit, the same self-administered drooling questionnaire was used to measure the scales post-injections. Post-injection complications were also recorded.

4.3.4 Drooling questionnaire

A drooling questionnaire developed by the senior author S.J.D with a multidisciplinary team of otolaryngologists, social workers, speech and language pathologists, and occupational therapists, validated elsewhere, was utilized. The questionnaire was divided into four categories: subjective drooling scales, objective drooling scales, impact of drooling on social life, and impact of drooling on physical health. Answers for each category were obtained at baseline and at 4 months after OBTXA injections. Each category contained several questions with a 5-point rating scale, where higher scores indicated more severe drooling. Some of these items were

similar to those used by others [41, 64, 158]. An additional section in the questionnaire was also created so that answers could be obtained at follow-up to evaluate family satisfaction and their desire to continue treatment.

4.3.4.1 Subjective drooling scales

Frequency and severity drooling scales were used for subjective assessment of the drooling before and after OBTXA injections. Frequency was scored out of 5, 1 indicating "none", to 5 indicating "constant, every day". Severity was also scored out of 5; 1 as "dry - no drooling", to 5 as "profuse - environment is wet".

4.3.4.2 Objective drooling scales

Three scales were used for objective assessment of drooling pre- and post-injections. The first scale measured the need for changing bibs/clothes due to drooling, with 1 indicating " none", 2 indicating "almost never", 3 indicating "sometimes", 4 indicating "often", and 5 indicating "almost always". A second question used the 5-point scale to describe the number of bibs/clothes changes per day, with 1 indicating "none", and 5 indicating "more than six times per day". The third question asked about the frequency of mouth wiping per day, with 1 indicating "none", and 5 indicating "more than 10 times per day".

4.3.4.3 Impact of drooling on social life

Four questions with a 5-point rating scale were developed to assess the impact of drooling on social life. These questions were related to the impact of drooling on the child's social life, the impact of the child's drooling on the family, the impact of the child's drooling on the community, and the impact of the child's drooling on the activities outside the home.

4.3.4.4 Impact on physical health

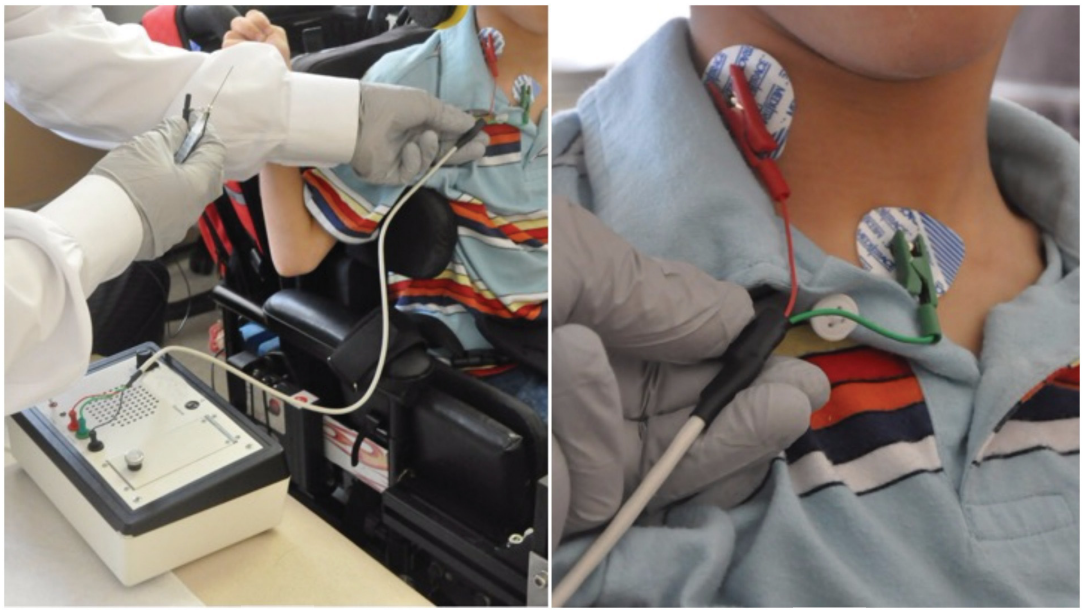
Four questions were created to evaluate the impact of drooling on the child's physical health. These questions asked about skin irritation of the face and neck, episodes of choking/aspiration, noisy breathing, and halitosis.

4.3.5 Caregiver satisfaction

Questions were asked about caregiver satisfaction after treatment, their subjective assessment of the improvement of drooling after treatment, and their desire to continue treatment after initial treatment. A 7-points rating scale was created to measure caregiver satisfaction; higher scores indicated higher satisfaction. An 8-point rating scale was also created to measure the child's improvement of drooling after the treatment, with higher scores indicating marked improvement. The desire to continue treatment was scored as yes or no.

4.3.6 Injection techniques

EMG-guided OBTXA injections were administered by an experienced otolaryngologist (S.J.D). All injections were performed in a clinical setting. Prior to injection, the skin was anesthetized with lidocaine 2.5% and prilocaine 2.5% cream. The skin was then cleaned with an alcohol swab. The EMG device picks up muscle action potentials when the needle is in muscle and is silent when the needle is inside a gland (Fig. 4.1). Ground and reference EMG electrodes were placed on the skin of the neck and chest (Fig. 4.1). The dose administered was calculated at 1 U/kg per gland to a maximum of 100 U, with both parotid and submandibular glands injected with the same dose. Each parotid gland was injected at two sites, directing the needle toward the tail of the parotid, between the sternomastoid muscle and the angle of the mandible (Fig. 4.2). The absence of muscle action potential was used to confirm the placement of the needle inside the parotid glands, avoiding injection of the superficial muscular aponeurotic system (SMAS) and the masseter muscle (Fig. 4.3). Each submandibular gland was injected at two sites by placing the needle percutaneously in the submandibular triangle, below the mandible (Fig. 4.2). The presence of positive action potential indicated either the platysma muscle superficially or the mylohyoid, hypoglossus, or digastric muscles deep to the submandibular gland. The absence of muscle action potential aided in confirming the placement of the needle inside the submandibular glands (Fig. 4.4).



A B

Fig. 4.1 A) EMG device that produces sound when muscle action potential is detected.
B) Ground and reference EMG electrodes were placed on the skin of the neck & chest.

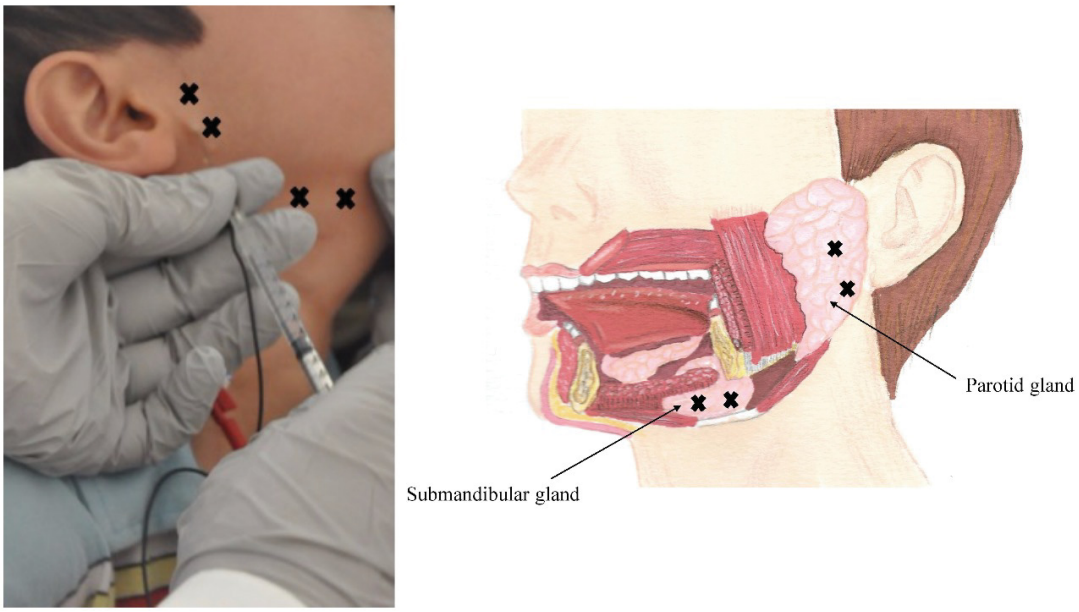


Fig. 4.2 Sites of OBTXA injections into the parotid and submandibular glands under EMG guidance (✖).

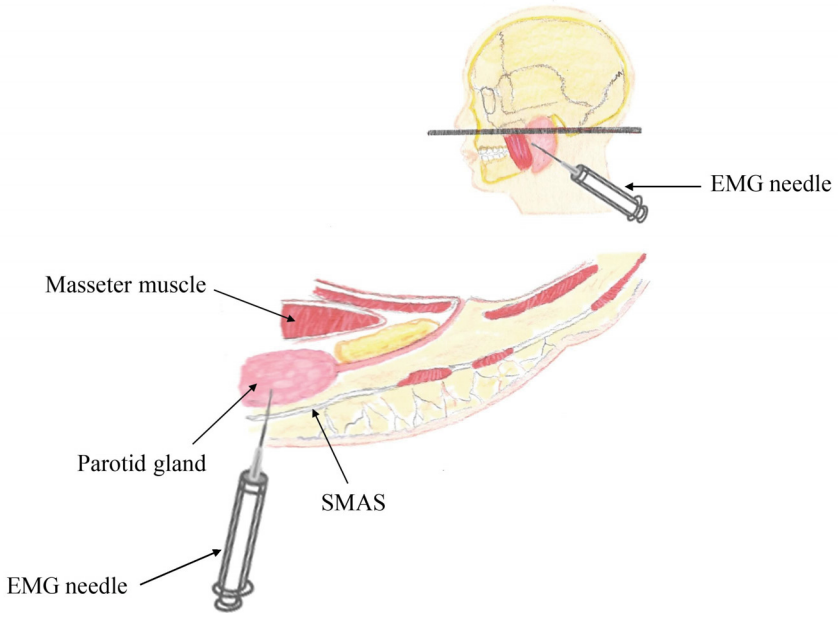


Fig. 4.3 A transverse cut section showing the placement of the Electromyography (EMG) needle inside the parotid gland avoiding the superficial muscular aponeurotic system (SMAS) and the masseter muscle.

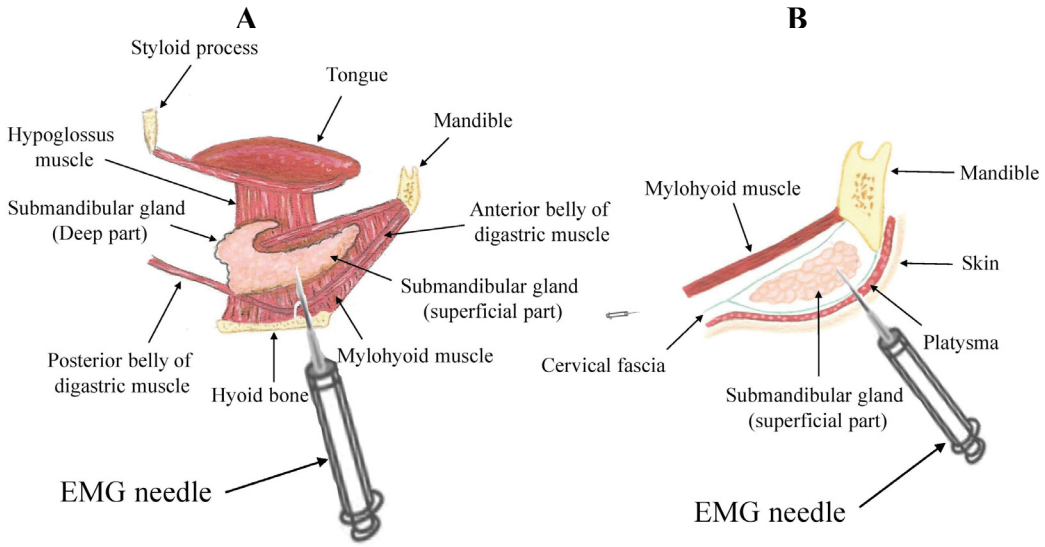


Fig. 4.4 A) A sagittal section showing the placement of Electromyography (EMG) needle inside the submandibular gland avoiding deep injection into the mylohyoid, digastric, and hypoglossus muscles.

B) A coronal section showing the placement of EMG needle inside the submandibular gland avoiding injecting superficially into the skin and the platysma muscle.

4.3.7 Statistical analysis

Data were analyzed by using the Statistical Package for the Social Sciences (SPSS) for Windows statistical software package, version 16.0. Descriptive statistics were calculated for all variables. Paired *t*-tests were used to compare each of the drooling questionnaire items pre- and post-injections. P-values ≤ 0.05 were considered to indicate statistical significance.

4.4 Results:

4.4.1 Patients' characteristics

A total of 26 children were enrolled in the study. Half of the children were male (50%) and the mean age was 8.7 years ± 4 (SD). Characteristics of the children are shown in Table 4.1. The majority of children had cerebral palsy (69.2%), while 30.8% had other underlying neurological disorders. An average follow-up between baseline and injection was 4.15 months ± 0.6 month.

Table 4.1 Demographic data of study participants.

Characteristics	EMG-guided OBTXA injections (n=26)
Age, y, mean ± SD	8.7 ± 4
Gender, no (%)	
Male	13 (50)
Female	13 (50)
Follow up, months mean ± months (SD)	4.15 ± 0.6

4.4.2 Sialorrhea outcome

Sialorrhea was considered to have been successfully managed (i.e., reduced) by EMG-guided OBTXA injections when a significant ($p \leq 0.05$) difference between baseline and post-injection scores was observed.

4.4.2.1 Subjective and objective drooling scales

As shown in Table 4.2, scores after EMG-guided OBTXA injections in all subjective and objective scales showed improvement after treatment. Significant decreases in drooling frequency (3.58 ± 1.06; P = 0.0001) and severity (3.08 ± 0.97; P = 0.001) were observed after EMG-guided OBTXA injections. The mean scores for the scales on the need to change bibs/clothes due to drooling, the number of bibs/clothes changes per day, and the frequency of mouth wiping per day after receiving EMG-guided OBTXA injections also significantly improved to 2.65 ± 1.38 (P = 0.05), 2.08 ± 1.59 (P = 0.004), and 3.04 ± 1.39 (P = 0.007) respectively (Table 4.2).

4.4.2.2 Impact of drooling on social life

Scores on the impact of drooling on the child's social life tended to improve (P = 0.23), as there was a 25% improvement after receiving EMG-guided OBTXA injections in children who scored "shy/embarrassed" or "shameful" at baseline. However, these scores did not reach statistical significance. The impact of drooling on the family's social life also showed a slight improvement after EMG injection (p = 0.52). Thirteen families (50%) scored "moderately/ a lot /isolation" at baseline. Only two of the 13 showed improvement on this score to "a little/not at all" after EMG injections (15.4% improvement; P = 0.52). However, scores on the impact of drooling on the community showed significant improvement (P = 0.0001), as 12 of 19 who scored " a lot/moderately" or "isolation" at baseline showed improvement (63.2% improvement). Scores on the impact of drooling on activities outside the home also showed significant improvement (P = 0.01), as seven of 16 who scored "severely/moderately/mildly" for this item showed improvement after EMG injections to "very mildly/no limitation" (43.75% improvement) (Table 4.2).

4.4.2.3 Impact of drooling on physical health

The results on skin irritation caused by drooling remained unchanged after EMG injections (P = 0.32). Three children had choking attacks once or twice due to drooling (11.5%). After EMG-guided OBTXA injections, choking improved in two of the three children, but this did not reach statistical significance (66.7% improvement; P = 0.16). Scores on drooling causing noisy breathing were the same at baseline and after EMG-guided injections (P = 0.86). Fourteen children suffered from halitosis at baseline (53.8%), and this improved in only two children after EMG-guided injections (14.3% improvement; P = 0.38) (Table 4.2).

Table 4.2 Comparison between scores of different drooling scales.

Variable drooling scales	**EMG-guided OBTXA injections (n = 26)**		**P value***
	Baseline **Mean ± SD**	Follow up **Mean ± SD**	
Subjective drooling scales			
Drooling frequency scale	4.4 ± 0.85	3.58 ± 1.06	**0.0001**
Drooling severity scale	3.54 ± 0.98	3.08 ± 0.97	**0.001**
Objective drooling scales			
Need to change bibs/clothes	2.96 ± 1.6	2.65 ± 1.38	**0.05**
Number of bibs/clothes changes per day	2.58 ± 1.6	2.08 ± 1.59	**0.004**
Number of mouth wiping per day	3.69 ± 1.19	3.04 ± 1.39	**0.007**

Impact on social life			
Impact on child's social life	2.4 ± 0.9	2.2 ± 1	0.23
Impact on the family	2.5 ± 1.1	2.3 ± 0.8	0.52
Impact on the community	3 ± 1.3	2 ± 1.2	**0.0001**
Impact on activity outside home	2.7 ± 1.2	2.3 ± 1.2	**0.01**
Impact on physical health			
Skin irritation of face and neck	2.3 ± 1	2.5 ± 1	0.32
Choking/ aspiration	1.12 ± 0.3	1 ± 0.2	0.16
Noisy breathing	1.6 ± 0.8	1.6 ± 0.9	0.86
Halitosis	1.7 ± 0.8	1.6 ± 0.7	0.38

* Paired *t*-test was used to compare the mean scores before and after the injection. P value ≤ 0.05 was considered to be statistical significant.

4.4.3 Caregiver satisfaction and complications after EMG-guided OBTXA treatment

After EMG-guided injections, six of 26 (23%) children showed marked improvement, 12 showed moderate improvement (46.2%), six showed slight improvement (23%), and two (7.7%) did not improve. On the 7-point rating scale, the mode for caregiver family satisfaction was 6, which corresponds to moderate satisfaction with the treatment. Seventeen families expressed moderate to marked satisfaction after receiving the treatment (65.4%) and seven were slightly satisfied (26.9%). Only two families were dissatisfied (7.7%). The majority of the families wanted to continue treatment; only one did not. In terms of complications post-injections, none were observed when EMG was used to guide OBTXA injections into the salivary glands.

4.5 Discussion:

To our knowledge, this is the largest prospective cohort study on EMG-guided OBTXA injections into the salivary glands of children with sialorrhea. This study showed that EMG was a useful tool to guide OBTXA injections, as it showed significant reduction in sialorrhea and resulted in no post-injection complications.

OBTXA works by inhibiting the release of acetylcholine at the nerve terminal, resulting in a reduction of saliva production [159]. OBTXA injections are usually guided either with manual palpation of the gland or with US [3, 18, 155, 160]. The recent literature has supported the use of EMG to guide OBTXA injections into a desired muscle group in cases with muscular spasticity [71, 156, 157]. However, studies on the use of EMG for guiding OBTXA injections into the salivary glands in children with sialorrhea are scarce. A case series of three children with familial dysautonomia, who received OBTXA injections under EMG guidance to manage their sialorrhea was reported by Daniel et al. [45]. Two of the three children received one session of EMG-guided OBTXA injections with an excellent response on the Teacher's Drooling scale and the Thomas–Stonell and Greenberg classification. The third child received five consecutive sessions of EMG-guided OBTXA injections for 15 months, with successful reduction of sialorrhea [45]. In the present study, the findings show that EMG-guided intra-glandular injections significantly reduced outcomes on the drooling frequency and severity scales, the need to change bibs/clothes, the number of bib/clothes changes per day, and the number of mouth wipes per day. These results agree with those of Savarese et al. [67]. However, the latter study used a different protocol on 19 children, whereby the parotid glands were injected only. Another 3-year retrospective study by Pena et al. showed an 83.3% improvement in 36 children after receiving ultrasound-guided injections in the submandibular glands and EMG-guided injections in the parotid glands [72]. However, they used EMG to guide injections only into the parotids, whereas in our study, we used EMG to guide the injections into both the parotid and submandibular glands. Moreover, the EMG technique they had used was based on observing facial twitches after delivering electrical stimulation to the facial muscles. In our study, we used a different technique, where confirmation of needle placement inside the glands was achieved by confirming the absence of EMG muscle action potentials. The only study that has used this technique to date was on adult amyotrophic lateral sclerosis patients with sialorrhea [69].

Overall, the findings of our study showed that drooling was reduced after EMG-guided OBTXA injections in 92% of the children, which is higher than that reported in previous studies (< 90%). This suggests that EMG-guided injections were better at delivering OBTXA to the body of the glands, resulting in significant improvement and better outcomes [6, 32, 60, 64, 72, 74, 75, 155]. Seventeen families expressed moderate to marked satisfaction after receiving the treatment (65.4%) and seven were slightly satisfied (26.9%). Only two families were dissatisfied (7.7%). Our results are consistent with the previous findings reported in the medical literature [67, 161]. Furthermore, based on the caregivers' perceptions, all children included in this study showed moderate to marked improvement after EMG-guided OBTXA injections. Only one family (3.8%) refused to continue treatment due to the lack of reduction in sialorrhea after receiving OBTXA injections.

In this study, a questionnaire was created to evaluate the effect of drooling on the child's and the family's social life. There was 25% improvement in the child's social life and 15.4% improvement in the family's social life after injecting OBTXA under EMG guidance, but these did not reach statistical significance (P = 0.23 and 0.52, respectively). However, the results were significant for the community (63.2% improvement) and on the child's activity outside the home (43.75% improvement) (P = 0.0001 and 0.01, respectively). We speculate that, due to the continuous care provided by the families to their drooling children, their social lives would remain affected, even after improvement. In terms of the effect on the community, improvement was observed as families tended to go outside their homes more often with their children after they showed significant improvement in sialorrhea caused by receiving EMG-guided OBTXA injections.

In terms of the impact of drooling on the child's physical health, results after EMG-guided injections were similar to baseline. There was no change in skin irritation of the face and neck, because although drooling was reduced, it did not decline enough to reduce skin irritation. Slight improvement was noticed in terms of reduced numbers of choking attacks and reduced halitosis, with 66.7% and 14.3% improvement, respectively, but these did not reach statistical significance (P= 0.16 and 0.38, respectively). Noisy breathing also did not change.

Complications following OBTXA injections can be classified into minor or major complications, based on the outcomes adopted by the Society of Interventional Radiology Potential [73]. Complications of OBTXA injections may include thick viscous saliva (3.9%), dryness of the mouth (3.3%), dysphagia (3.3%), and pneumonia (2.2%). Other complications include flu-like symptoms, difficulties in swallowing and chewing, weakness of the masseter muscles and, rarely, jaw dislocation [58, 62, 162-165]. Another possible complication is injury to the facial nerve, which has not been reported in children [60]. In the current study, there were no complications observed, similar to the results reported by Daniel et al., Pena et al., and Savarese et al. when they used EMG to guide OBTXA injections [45, 67, 72]. Thus, this finding suggests that EMG guidance might help to avoid complications post-OBTXA injections.

Several study limitations are worth noting. Caregiver's reporting bias is also expected because of the use of subjective questionnaires. However, the use of objective measures is much less affected by this bias. Other limitations are the small number of patients enrolled in the study and the lack of a comparison group in which other injection techniques were used. This supports the need for a randomized controlled trial to provide stronger evidence of efficacy and safety of EMG-guided OBTXA injections. Due to the lack of accurate objective measurements in the field of sialorrhea, we have used a combination of subjective and objective scales to overcome this limitation and to provide reliable and valid results. Despite these limitations, this is the largest cohort study in which treatment outcomes and complications after EMG-guided OBTXA injections in children with sialorrhea were measured. The authors believe that the findings of this study provide evidence that EMG-guidance is a safe and effective method of guiding OBTXA injections into the salivary glands in children with sialorrhea.

4.6 Conclusion:

The results reported suggest that EMG-guided OBTXA injections have a significant impact on drooling outcomes without any complications post-OBTXA injections. Further randomized double-blinded clinical trials with a larger number of subjects and a longer follow-up are required to confirm the usefulness and the safety of EMG-guidance of OBTXA injections.

4.7 Linking statement:

The previous study on EMG-guided OBTXA injections showed a significant reduction of sialorrhea in children, without complications. However, one of the limitations of the use of OBTXA in the treatment of sialorrhea is the possible development of a neutralizing antibody against OBTXA, resulting in secondary non-response to intra-glandular OBTXA injections. The next chapter discusses this topic and how to manage it by presenting a case report, which described a patient who developed secondary non-response of intra-glandular OBTXA injections while being treated for sialorrhea.

Chapter 5: Secondary non-response of Intra-glandular Onabotulinumtoxin A injection in a child with sialorrhea

(Manuscript 3)

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5.1 Abstract

Sialorrhea is common in children with chronic neurological disorders. Injections of Onabotulinumtoxin-A (OBTXA) into the salivary glands is an effective treatment option. However, repeated injections are required. However, there is a risk of forming neutralizing antibodies against OBTXA with the long-term use, leading to treatment failure.

We report the case of a 12-year old patient with severe sialorrhea managed by intra-glandular OBTXA injections. After 2 years of treatment, the patient became a non-responder. After cessation of the injections for 1 year, injections were resumed and the patient began to show improvement, without evidence of further resistance.

5.2 Introduction

Sialorrhea (drooling) is defined as unintentional discharge of excessive saliva from the mouth due to either decreased clearance or excessive production [74]. Sialorrhea can lead to medical, clinical, and social problems that have a negative impact on the quality of life of affected children and their families [35, 46].

Sialorrhea is best managed by a multidisciplinary team approach [46]. Treatment options include oral motor therapy, behavioral therapy, anticholinergic medications, and surgery. Recently, intra-salivary glandular Onabotulinumtoxin-A (OBTXA) injections, which were first reported by Bushara in 1997, have been proven effective for sialorrhea control [33, 64, 166].

However, as OBTXA injections for sialorrhea have come into wider use, cases of therapy failure after multiple injections have also been reported [167, 168]. The production of neutralizing antibodies against botulinum toxins has been cited as a main reason for these treatment failures, and several treatment strategies have been identified to overcome production of these antibodies [168, 169]. However, to date, there are no clear guidelines regarding management of OBTXA resistance. We report a case of a 12-year-old patient with sialorrhea managed with OBTXA injections, who developed resistance to the injections, and we discuss the management of OBTXA resistance.

5.3 Clinical case

The female patient presented at 12 years of age with cerebral palsy, Moya Moya disease, global developmental delay, and history of renal failure for which kidney transplant was performed at 10 years of age. The patient had excessive salivation associated with repeated choking episodes that interfered with feeding. On examination, the patient had poor oral motor control and poor head posture, which exacerbated the sialorrhea. Treatment with electromyography (EMG)-guided intra-salivary gland OBTXA injections was initiated, with injections given every 6 months. The patient had 5 successful injections over 2 years and showed an excellent clinical response without any complications. She also received OBTXA injections in

the biceps muscles and hips to manage spasticity in accordance with orthopedic recommendations.

After the 6th injection (2 years after initiating the treatment), the patient became a non-responder, and 3 additional trials using the same technique and a higher dosage were not helpful. A test with 10 units of OBTXA in a forehead wrinkle confirmed the lack of response in this patient, with persistence of the wrinkle. It was decided to withhold injections for a year, during which the patient was managed with oral anticholinergic medications. A year later, the patient was reinjected with OBTXA with a good clinical response and has received 3 additional injections to date, with good results.

5.4 Discussion

Botulinum toxin is a protein produced by *Clostridium botulinum* that inhibits the release of acetylcholine from the cholinergic nerve terminal, leading to decreased muscular activity [170, 171]. Intra-salivary gland OBTXA injections have proven to ameliorate sialorrhea. However, increasing use of OBTXA for sialorrhea has been accompanied by cases of resistance leading to secondary treatment failures [167, 170, 172, 173].

Dressler has classified OBTXA treatment failures into different categories, including primary therapy failure, in which there is no response to OBTXA from its first application; secondary therapy failure, in which the patient fails to respond after initial treatment success; and temporary therapy failure, in which only singular injection series fail [173]. Based on this categorization, our patient had secondary temporary therapy failure.

There are various risk factors for secondary treatment failure. These include injection technique, experience of the injection provider, change of dosing, inappropriate injection site, and disease progression [174]. However, antibodies against OBTXA are thought to be the main cause of resistance [170, 173]. In previous reports, 5 to 17% of patients with cervical dystonia developed resistance with original OBTXA injections [168, 175], and approximately 1% of patients with low immunogenicity will develop resistance to OBTXA [176].

There are two forms of anti-OBTXA antibodies, neutralizing (directed against the botulinum neurotoxin component) and non-neutralizing [177]. Risk factors for developing neutralizing antibodies include high doses of OBTXA, short interval between injections (<3 months), booster injections (<6 weeks between injections), high total cumulative dose, and young age [170, 178, 179]. Detection of anti-OBTXA antibodies can be carried out by functional and laboratory tests, although the sensitivity and specificity of these tests have not been determined. Functional tests include frontalis test, sternocleidomastoid test, and extensor digitorium brevis test, and laboratory tests include mouse lethality assay, mouse protection assay, and mouse phrenic nerve-hemidiaphragm preparation. The persistence of resistance after formation of anti-OBTXA antibodies remains unclear [180, 181].

Several strategies have been identified to manage resistance. Different forms of botulinum toxin, such as botulinum toxin B (BTX-B), can be substituted for OBTXA. However, cross-reactions may occur with this method [170, 182]. Berweck et al. demonstrated the possibility of cross-reaction in a report of a child with cerebral palsy who suffered from sialorrhea and was treated with BTX-B injections into the salivary glands [183]. The patient showed no response after 3 successful sessions and mouse diaphragm assay (MDA) confirmed the presence of antibodies against BTX- B. Subsequent injections with OBTXA did not show any clinical response, even though, there was no evidence of antibodies against OBTXA by MDA. Increasing the dose of OBTXA has been proposed as a means of overcoming resistance, but its efficacy has not yet been determined [184]. In the present case, the patient did not respond to three trials of an increased OBTXA dose.

Dressler has reported spontaneous disappearance of anti-OBTXA antibodies after cessation of OBTXA injections [173], and other authors have also reported this phenomenon. In one study, antibodies against OBTXA disappeared in half of the patients within one year after cessation of OBTXA injections [185]. In another study, 7 patients showed no evidence of antibodies after a period of 10 to 78 months [186]. Similarly, in our case, a clinical response returned after withholding OBTXA treatments for one year.

5.5 Conclusion

Sialorrhea affects children with neurological disorders. OBTXA injection into the major salivary glands has been demonstrated to be an effective treatment to reduce sialorrhea and improve of the patient's and family's quality of life. Secondary non-response is thought to be related to antibodies against OBTXA, which might occur as a result of frequent and long-term use of OBTXA injections. Identifying risk factors for development of OBTXA antibodies will be essential to identify secondary non-responsiveness, and further studies are required to clarify the optimal management approaches in cases of OBTXA resistance. In the case presented here, cessation of OBTXA for a year after the development of OBTXA resistance was effective in restoring the effect of OBTXA.

Chapter 6: Overall Discussion and Conclusion

6.1 Linking statement from manuscripts

Chapter 2 showed that Botulinum Toxin/Onabotulinum Toxin-A (BTX/OBTXA) injections are an effective treatment option for sialorrhea. Chapter 3 presented a narrative comprehensive review that showed that EMG is useful in many clinical conditions in otolaryngology–head and neck surgery. It can help in the diagnosis and prognosis in cases of vocal fold immobility disorders and facial nerve paralysis. Moreover, it can facilitate monitoring of vulnerable nerves, such as the recurrent laryngeal nerve and facial nerve in various types of head and neck surgery. The review also showed that EMG aids in directing BTX injections in cases of adductor laryngeal breathing dystonia, palatal myoclonus and sialorrhea.

Many studies have advocated guiding BTX injections inside the salivary glands to avoid injection into the muscles, which can lead to therapy failure and potential complications. EMG is one of the techniques for guiding BTX injections. The concept of using EMG is to ensure needle placement inside the salivary glands by detecting motor unit action potentials (MUAP) from the muscles overlying or deep to the glands. This technique has been used in adults with amyotrophic lateral sclerosis [69], with few reports of its use in children [45, 67, 72]. Therefore, our study is described in Chapter 4 is the largest study on treatment outcomes and complications of EMG-guided BTX injections in children with sialorrhea. Our study showed a significant improvement in sialorrhea after EMG-guided BTX injections across all subjective and objective outcome measurements scales. Moreover, the child's and family's social lives improved, as did the child's physical health, although these did not reach statistical significance.

Post BTX injections, complications, such as thick saliva, chewing and swallowing problems, and, more seriously, aspiration pneumonia, may occur. However, we found no such complications in our study. Additionally, one of the limitations of using BTX is the possibility of developing BTX antibodies, leading to secondary non-response to BTX injections, as reported in chapter 5. Temporary cessation of BTX treatment after the development of clinical resistance may be effective in restoring the effect of BTX.

6.2 Relation to other studies

Only three previous studies have used EMG to guide BTX injections in children. These are a case series by Daniel et al. on three children with familial dysautonomia [45], another retrospective study by Pena et al. on 36 children [72], and a prospective study by Savarese et al. on 19 children with sialorrhea [67]. All these studies used EMG to inject BTX into the parotid glands only. In our study, described in chapter 4, we used EMG to guide BTX into both the parotid and submandibular glands. Moreover, Savarese and Pena used a different EMG techniques from the one used in our study. Whereas Savarese et al. did not clearly describe the EMG technique that was used on their children, Pena used different technique to guide injections by utilizing an EMG needle to stimulate the facial muscles electrically to detect facial muscle twitches as a means to avoid injury to the facial nerve. In our study, we used EMG to detect MUAP, using sounds associated with EMG due to MUAPs from the muscles overlying and deep to the salivary glands to ensure that BTX was injected into the salivary glands, and not into the surrounding muscles. Therefore, to our knowledge, this is the largest study to measure treatment outcomes and complications of EMG-guided BTX injections in children with sialorrhea by detecting MUAP. Our study showed a significant improvement in sialorrhea after EMG-guided injections, without post-injection complications.

6.3 Limitations

There were several limitations in our study. The lack of accurate objective measurements, which can reflect the improvement and treatment outcomes after BTX injections more precisely, is the central limitation of this study. However, a combination of subjective and objective scales was used to overcome this limitation and to provide reliable and valid results. Another limitation is the lack of a comparison group using different techniques, such as ultrasound guidance. Despite these limitations, we believe that the findings of this study provide the evidence that EMG-guidance is a safe and effective method for injecting BTX into the salivary glands of children with sialorrhea.

6.4 Future directions

A randomized double-blinded controlled trial with both subjective and more accurate objective measurements is required to provide evidence for the efficacy of EMG-guided BTX/OBTXA injections. This follow-up study should compare EMG with ultrasound-guided injections, which is considered to be the gold standard guidance technique

6.5 Overall conclusion

EMG has various clinical uses in pediatric otolaryngology, including treatment of sialorrhea. Moreover, this thesis has shown that sialorrhea was significantly reduced in children who received EMG-guided BTX injections, with no complications. Thus, the study provides preliminary evidence of the efficacy and safety of EMG-guided BTX injections in children with sialorrhea. However, the frequent and long-term use of OBTXA injections may lead to the formation of neutralizing antibodies and secondary non-response to OBTXA. As shown in a case study, cessation of OBTXA injections for 1 year may be helpful in resuming the efficacy of OBTXA.

6.6 Claims of originality

This is the largest study to utilize EMG to guide BTX injections into the salivary glands in children with sialorrhea, by detecting MUAP from the muscles overlying and deep to the salivary glands.

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