Sialorrhea in Parkinson’s Disease

Subjects: Pathology

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Sialorrhea, or excessive saliva beyond the margin of the lip, is a common problem in many neurological diseases. Previously, sialorrhea has been underrecognized in Parkinson’s disease (PD) patients. Despite this, many patients rank sialorrhea as one of the most debilitating complaints of Parkinson’s disease. Previous treatment for sialorrhea has been suboptimal and has been plagued by significant side effects that are bothersome and can be dangerous in patients with a concurrent neurodegenerative disease. This review sought to review the anatomy, function, and etiology of sialorrhea in PD. It then sought to examine the evidence for the different treatments of sialorrhea in PD, and further examined newer evidence for safety and efficacy in minimally invasive treatment such as botulinum toxin.

Keywords: sialorrhea ; botulinum toxin ; Parkinson’s disease ; drooling ; Abobotulinumtoxin A ; Incobotulinumtoxin A ; Onabotulinumtoxin A ; Rimabotulinumtoxin B

1. Introduction

Sialorrhea, commonly referred to as drooling, is defined as excessive saliva beyond the margin of the lip. Sialorrhea is caused by either hypersalivation or problems with the removal of saliva considered abnormal after the age of 4. It is a common neurological manifestation of many neurological diseases including cerebral palsy (CP), Parkinson’s disease (PD), and amyotrophic lateral sclerosis (ALS) [1]. Drooling can be a devastating and debilitating complication of PD and is one of the most prevalent complaints of patients. It is often underrecognized and undertreated. Some estimates show that up to 80% of patients with Parkinson’s disease experience sialorrhea [2]. In advanced PD, it is among the three most common complaints from patients overall [3]. Drooling is very problematic and can lead to sheer embarrassment, social isolation, depression, skin infection, malodor, and aspiration pneumonia [4]. Accumulation of secretions puts patients at an increased risk of aspiration of the products, and thus can lead to significant morbidity and mortality associated with aspiration pneumonia in patients with PD [5]. Aspiration pneumonia carries around a 20% mortality in PD patients [6].

2. Etiology of Sialorrhea in Parkinson’s Disease (PD)

Initial hypotheses suggested that sialorrhea was attributable to an excessive production of saliva secondary to autonomic dysfunction, but further sialometry studies showed that production was actually reduced in PD versus non-PD patients [7]. Thus, thought shifted to the likely etiology being a decreased ability to swallow, thereby interfering with the clearance of saliva, which is reliant upon adequate muscle coordination to initiate the swallow reflex. There are three phases to swallowing: an oral phase under voluntary control, a pharyngeal phase, and an esophageal phase, where the latter two are under involuntary control. One study by Umemoto et al. evaluated quantitative video-fluoroscopic images of PD patients to demonstrate if the oral phase worsened with the progression of PD [8]. They measured the speed of movement of barium gelatin jelly and the associated range of motion of oropharyngeal muscles. The study result showed that maximum tongue pressure was significantly larger, and oropharyngeal transit time was significantly shorter in mild to moderate (Hoehn and Yahr stages II and III) PD versus advanced (Hoehn and Yahr stages IV and V) PD. They also found a significant negative correlation between the speed of oropharyngeal muscle movement and the resulting transit time, which reinforced the hypothesis that impaired oropharyngeal transport and reduced swallowing frequency lead to oral phase deterioration [8]. Additional studies associated sialorrhea with higher UPDRS motor scores, loss of motor function, and progression of PD. Thus, the current literature suggests sialorrhea is likely caused by a combination of oropharyngeal bradykinesia and inability to clear salivary secretions, which together lead to the excessive pooling of saliva seen in PD patients [9].

3. Botulinum Toxin in Sialorrhea

Botulinum toxin has class A evidence in the treatment of sialorrhea. Both botulinum toxin A and B have been used in the treatment of sialorrhea, and have been shown to have fewer side effects than comparative treatment [10]. By injecting botulinum toxin locally into the salivary glands, the production of saliva is reduced, and the risks of systemic effects are limited. Botulinum toxin A was first used by Pal et al., who showed a marked improvement in the reduction of saliva and a 66% subjective improvement in patients [11]. In 2004, a study by Ondo et al. showed similar efficacy of botulinum toxin B in the treatment of drooling [12]. Further pivotal studies have led to botulinum toxins becoming FDA-approved therapies for the treatment of sialorrhea, particularly serotypes IncobotulinumtoxinA (07/0218) and RimabotulinumtoxinB (08/2019).

The therapeutic uses of botulinum toxin A and B are well recognized and rapidly expanding. There are three botulinum A toxins: AbobotulinumtoxinA, IncobotulinumtoxinA, and OnabotulinumtoxinA, and one botulinum B toxin, RimabotulinumtoxinB. Each work in slightly different ways and have different indications. All four agents differ in complexity, purity, potency, dosing, and immunogenicity [13]. Key differences between the four major botulinum toxins are listed in the Table 1 below.

Table 1. Comparing the four major botulinum toxins.

Toxins	Brand Name	Indication	Company	Clinical Trial	Dosage	Side-Effect/Cons
Botulinum toxin A						
IncobotulinumtoxinA	**Xeomin**	**FDA-approved for chronic Sialorrhea**	**Merz Pharmaceuticals (Germany)**	**SIAXI**	**100 U**	**Dry mouth, dysphagia [14]**
OnabotulinumtoxinA	**Botox**	**No FDA approval for Sialorrhea**	**Allergan US**		**-**	**Unknown**
AbobotulinumtoxinA	**Dysport**	**No FDA approval for Sialorrhea**	**Ipsen (France)**		**-**	**Unknown**
Botulinum toxin B						
RimabotulinumtoxinB	**Myobloc**	**FDA-approved for chronic Sialorrhea**	**Myobloc (USA)**	**Isaacson et al.**	**2500 U and 3500 U**	**Dry mouth, dysphagia, and dental caries [15]**

4. Techniques

There are two main accepted ways for localization of the salivary glands for botulinum toxin treatment: anatomical or ultrasound guided. The ultrasound guided approach targets the maximum gland thickness, whereas the anatomical approach uses known landmarks and positioning based on published recommendations. For parotid gland localization, the FDA recommended approach is to locate the midpoint between the tragus and the angle of the mandible, and to deliver an injection 1 cm anterior to this point. For the submandibular gland anatomic localization, the recommendation is to find the midpoint between the angle of the mandible and the tip of the chin and to inject 1 finger breadth medial to the inferior surface of the mandible.

Both are approved approaches, although some argue that an ultrasound guided approach may allow for more accurate injection into the gland [16]. In some studies, the success rate for salivary gland injection via anatomical landmark of parotid and submandibular glands ranged from 30 to 70%. The success rate varied greatly based on population, type of study, which glands were targeted, dosage, and level of training and technique. In another study, the accuracy of anatomical versus ultrasound guided approaches into the parotid gland in cadavers was 79% to 96%, respectively, although the results were not statistically significant. They also found the accuracy of anatomical versus ultrasound guided injection into the submandibular gland to be 50% to 91%, respectively, and the results were statistically significant. This study thus concluded that the ultrasound guided approach was more accurate when compared with the anatomical approach for submandibular gland injections [17]. While in some cases, the ultrasound method was shown to be both safe and effective, there has yet to be a large-scale clinical trial evaluating the superiority of the ultrasound guided approach over the anatomical landmark approach.

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