Critical Review: The Effectiveness of Botulinum Toxin as Treatment for Drooling among Patients with Parkinson's Disease.

Butler, L.
M.Cl.Sc. (SLP) Candidate
School of Communication Sciences and Disorders, U.W.O.

This critical review examines the effectiveness of botulinum toxin as treatment for drooling among patients with Parkinson's disease. Studies using within-subjects experimental designs and randomized controlled trials were analyzed to determine the effects of botulinum toxin on drooling associated with Parkinson's disease. Overall, the literature supports the use of botulinum toxin for treatment of drooling among patients with Parkinson's disease.

Introduction

Parkinson's disease (PD) is a progressive idiopathic neurological disease that affects approximately 50 people per 100,000 over the age of 50 with the average age of onset being 55 years (Duffy, 2005). Parkinson's disease is caused by deterioration of the dopamine producing neurons in the brain stem and basal ganglia, particularly in the substantia nigra (Duffy, 2005). The major symptoms of PD include rest tremor, akinesia, rigidity, and loss of postural reflexes.

Dysphagia is a common symptom of PD with different types of swallowing difficulties corresponding to different stages of the disease. Sialorrhea, or drooling, is one swallowing-related difficulty that affects approximately 75% of all patients with PD (Proulx et al., 2005). It is believed that drooling in patients with PD is a result of swallowing dysfunction, specifically saliva pooling in the mouth due to reduced swallow frequency, not increased saliva production (Marks, 2001). It is thought that the head down posture characteristic of PD, along with reduced oral motor control and decreased awareness, contribute to drooling. Drooling of saliva can result in aspiration, chest infections, angular chelitis due to candidal infection, speech problems, and psychosocial issues for patients and caregivers. In addition, drooling has been related to embarrassment, reduced social interaction, and decreased quality of life (Dogu et al, 2004). Some patients with PD report drooling to be the worst symptom of the disease (Ondo, Hunter, & Moore, 2004).

Current treatments for drooling associated with PD include anticholinergic drugs, surgical procedures, and radiation. Anticholinergic drugs, which block the action of acetylcholine, have been found to reduce salivary secretion; however, they are associated with many side effects including confusion, memory problems, hallucinations, blurred vision, urinary retention, and cardiac arrhythmia (Dogu et al., 2004). Surgical procedures include gland resection, transposition of the excretory ducts, and tympanic neurectomy. These procedures, as well as irradiation of the salivary glands, are invasive and therefore are typically not accepted by patients (Dogu et al., 2004). Due to the unsatisfactory results of the above treatments, Bushara (1997) first proposed the use of botulinum toxin A (botox) for treatment of drooling in patients with amyotrophic lateral sclerosis (ALS).

Botulinum toxin A comes from the highly poisonous bacteria *Clostridium botulinum*. It works by blocking the release of acetylcholine at the presynaptic level (Bushara, 1997). The blockage is irreversible; however, recovery occurs after approximately three months due to re-sprouting of axons and formation of new acetylcholine receptors. The major symptoms of botulism, a rare illness caused by the bacteria, are muscle paralysis and dysfunction of the autonomic nervous system. In addition, dry mouth is a common symptom, occurring in approximately 93% of patients with botulism. The salivary glands are under autonomic control and should therefore be susceptible to inhibition by botox (Bushara, 1997).

Botox injections are currently used to treat blepharospasm, hemifacial spasm, spasmodic torticollis, and other dystonic disorders (Bushara, 1997). Some minor side-effects have been found following botox injections, including temporary local swelling and bruising at the

injection site, and spread of the toxin causing temporary weakness of nearby muscles (e.g. ptosis, dysphagia); however, these side-effects are usually well tolerated by patients. Dry mouth has also been reported as a side-effect of botox injections for spasmodic torticollis, indicating inhibition of the salivary glands (Bushara, 1997).

Objectives

The objective of this review is to critically examine the literature to determine the effects of botox on drooling among patients with PD. A further objective of this review is to provide recommendations, based on the reviewed literature, regarding the use of botox as treatment for drooling associated with PD.

Methods

Search Strategy
Computerized databases, including PubMed, Medline, and CINAHL, were searched using the following search strategy:

> ((drooling OR sialorrhea) AND (Parkinson's disease) AND (botulinum toxin))

The search was limited to articles written in English between 1980 and 2006.

Selection Criteria
Studies selected for inclusion in this critical review paper were required to investigate the effects of botox on drooling among patients with PD.

Data Collection
Results of the literature search yielded two within-subject experimental design studies and four randomized controlled trial (RCT) design studies.

Results

Pal et al. (2000) conducted a within-subject experimental design of 9 patients with PD and drooling in which amount of drooling was compared before and after botox injections in the management of drooling associated with PD. Amount of drooling was measured objectively using dental rolls to measure saliva production and subjectively through the use of questionnaires. It was unclear how the results of the study were analyzed. The authors found that 6 out of 9 patients reported subjective improvement in drooling and all but one patient experienced an objective reduction in saliva. One patient reported transient pain at the site of injection. The significance of these results is unclear. The authors concluded that botox can be a safe and simple treatment method for drooling associated with PD; however, a double-blind RCT study is needed. Based on the critical appraisal this article provides moderate evidence for the use of botox as treatment for drooling associated with PD.

Friedman and Potulska (2001) conducted a within-subject experimental design of 11 patients with PD and drooling in which amount of drooling was compared before and after botulinum toxin injections in the management of drooling associated with PD. Amount of drooling was measured objectively using dental rolls to measure saliva production and subjectively through the use of questionnaires. Results were analyzed using a paired comparison student t-test for within-subject data. The authors reported significant subjective and objective improvement in drooling in 9 out of 11 participants. No side effects were observed in any patient. Overall, Friedman and Potulska (2001) concluded that botox is an effective treatment for drooling associated with PD. Based on the critical appraisal this article provides moderately strong evidence for the use of botox as treatment for drooling associated with PD.

Lagalla et al. (2006) describe a double-blind RCT study of 32 patients (16 control; 16 treatment) with PD and drooling in which botox injections were compared with a placebo (i.e. saline solution) in the management of drooling associated with PD. Amount of drooling was measured objectively using dental rolls to measure saliva production and subjectively through the use of questionnaires. Results were analyzed using an unpaired t-test for parametric data, the Mann-Whitney U test for nonparametric continuous data, the Fisher's exact test, and the test of proportions for category data. A two-way analysis of variance (ANOVA) for repeated measures and an odds ratio were also used. The authors reported a statistically significant improvement in almost all objective and subjective measures for the botox group as well as no change in the placebo group. One participant in the botox group reported mild

transitory swallowing difficulties. Overall, Lagalla et al. (2006) concluded that botox injections can be considered an effective treatment for drooling associated with PD. Based on the critical appraisal this article provides strong evidence for the use of botox as treatment for drooling associated with PD.

Mancini et al. (2003) describe a double-blind RCT study of 20 patients (10 control; 10 treatment) with PD (n=14) or Multiple System Atrophy (n=6) and presence of drooling in which botox injections were compared with a placebo in the management of drooling associated with parkinsonism. Amount of drooling was measured subjectively through the use of questionnaires. Results were analyzed using the chi-square test, the Wilcoxon matched-pairs signed-ranks test, the non-parametric Wilcoxon two-sample test, and the Pearson correlation. The authors reported a significant reduction in drooling for the botox group at two weeks post-treatment; however, no differences were found at three months post-treatment. No adverse effects were reported other than a painful sensation during needle insertion. Mancini et al. (2003) concluded that botox is a safe and effective treatment for drooling in parkinsonism. Based on the critical appraisal this article provides moderate evidence for the use of botox as treatment for drooling associated with PD.

Lipp et al. (2003) describe a double-blind RCT study of 32 with various diagnoses (12 patients with PD) and drooling in which various doses of botox injections were compared with a placebo in the management of drooling. Amount of drooling was measured objectively using dental rolls to weigh saliva production and subjectively through the use of questionnaires. Results were analyzed using a non-parametric ANOVA. The authors reported an objective reduction in saliva for all botox groups as compared to the placebo group; however, the difference was only found to be significant in the high dose group. Overall, Lipp et al. (2003) concluded that botox may be an effective treatment for drooling; however, that more studies examining higher doses of botox are needed. Based on the critical appraisal this article provides moderate evidence for the use of botox as treatment for drooling associated with PD.

Marks et al. (2001) describe a RCT study of 28 patients with PD in which botox injections were compared with a speech and language therapy (SLT) intervention in the management of drooling associated with PD. It was unclear how many participants were assigned to each group. Amount of drooling was measured objectively by weighing stimulated saliva production and subjectively through the use of questionnaires. It was unclear if any statistical tests were used to analyze the data. The authors reported a subjective reduction in drooling severity for both the botox and SLT groups at one month post-treatment. The authors reported that some participants stated that the botox injections were painful. No objective results were provided. It is unclear if any of these results are significant. Based on the critical appraisal this article provides weak evidence for the use of botox as treatment for drooling associated with PD.

Discussion

Subject Selection

All of the analyzed studies, with the exception of Lipp et al. (2003), provided some demographic information of participants. Demographic characteristics of are important when attempting to generalize research findings. In this population it is very important because the length of disease duration or the stage of PD can influence treatment results. Pal et al. (2000) began their study with seven participants and recruited two additional participants following the first botox injection; no rationale was provided for the additional subjects.

Mancini et al. (2003), Lipp et al. (2003), and Marks et al. (2001) recruited patients with PD from a movement disorders outpatient clinic. It was unclear how participants were identified and recruited in the remaining studies. The identification of participants is important as there can be inherent differences between groups of participants depending on how they are selected (e.g. volunteers vs. non-volunteers) which can influence the results of a study.

The six studies all described some inclusion/exclusion criteria for participants. These parameters are important as they serve to control for confounding variables that could influence the results. All studies, except for the study by Mancini et al. (2003), controlled for other anti-drooling medications during the course of the study. This is an important variable as other anti-drooling medication could interfere with the effects of botox injections.

Mancini et al. (2003) and Lipp et al. (2003) included patients with PD as well as patients with other diseases in their studies. This was appropriate as the purpose of both studies was to assess the efficacy of botox on drooling in general, not within a certain population. However, for the purpose of this analysis the inclusion of a variety of diagnoses decreases the strength of the study for determining the usefulness of botox for drooling associated specifically with PD.

Methodology

Five of the six studies included highly detailed descriptions of the procedures used for botox injections. Marks et al. (2001) provided highly detailed descriptions of their SLT intervention; however, no information was provided on the procedure used for botox injections. It is unclear from the article how much botox was injected into the participants in the botox group. It is important for authors to provide detailed descriptions of procedures in order for the study to be replicated.

Participants in the study by Pal et al. (2000) were injected with two different doses of botox eight weeks apart. The authors did not provide a rationale for the second higher dose of botox only eight weeks after the first dose. There was no evidence to suggest that the effects from the first injection had worn off after eight weeks. Therefore, any measures taken following the second injection may have been confounded due to lasting effects from the first botox injection.

Measurement Tools & Outcome Measures

Five out of the six analyzed studies performed subjective and objective outcome measures. Objective measures for four of the five studies involved weighing dental rolls to measure amount of saliva produced. The process of weighing dental rolls was fairly well described in all studies; however, the number of dental rolls used was inconsistent throughout the studies. More consistent procedures would allow for comparisons across studies. It is questionable whether measuring total saliva production is a valid measure of amount of drooling. In order to enhance reliability, Pal et al. (2001), Lagalla et al. (2006), and Lipp et al. (2003) measured saliva production twice and used the average of the two repeated measures for analysis.

In contrast to the above studies, Marks et al. (2001) measured stimulated saliva flow as an objective outcome measure. The authors did not provide a rationale for measuring stimulated saliva flow as opposed to saliva flow at rest. As the purpose of this study was to measure amount of drooling it would have been more valid to also include a measure of saliva flow at rest as drooling is not restricted to times when salivary flow is stimulated. Mancini et al. (2003) did not perform any objective measures of salivary flow which would have enhanced the validity of their study.

Subjective measures for all six studies consisted of rating scales completed by the participants to indicate severity/frequency of drooling. All subjective measures appeared to have face validity for measuring amount of drooling; however, this was not discussed by any of the authors. Pal et al. (2000), Lagalla (2006), and Mancini (2003) assessed the presence of adverse effects in subjective measures; it was unclear if this area was evaluated by the other studies. The presence of adverse effects should be an important part of determining the usefulness of botox for treatment of drooling in patients with PD.

Statistical Analysis

Three of the six studies described and employed appropriate statistical tests to analyze data (Friedman & Potulska, 2001; Lagalla et al., 2006; Mancini et al., 2003).

It was difficult to assess the appropriateness of the statistical analysis performed by Pal et al. (2001) as it was unclear which tests were used. The authors of this study did not describe any statistical tests; however p-values were provided suggesting that some form of statistical analysis was performed. A paired comparison t-test would be an appropriate test to analyze the data in this study as this test is designed to compare two sets of observations on a single sample.

Lipp et al. (2003) performed an analysis per protocol due to the rapid progression of some of the diseases of participants in the study. The endpoints of the study were reported to be the time when a significant decrease of drooling was seen in the botox group compared to the control group as measured by dental rolls or when significant differences were seen in the subjective measures. This procedure is problematic as the study could continue indefinitely and participants would likely be followed for different lengths of time, as was the

case in this study (i.e. some patients followed for three months and some for six months).

Marks et al. (2001) did not appear to use any statistical tests to analyze the data.
Raw data was provided for the subjective drooling rating scale; however, no data was provided from the objective measurement of stimulated saliva flow. Based on the information in the article, it is unclear whether or not the differences in drooling observed between the groups were significant. A two-way analysis of variance (ANOVA) for repeated measures could have been used in this case to test both within-subject and between subject changes in outcome measures.

Recommendations

It is recommend that botox injections should be used in clinical practice for treatment of drooling among patients with PD. All six studies, despite some methodological flaws, provide support for the use of botox injections among this population.

Future research should involve more double-blind RCT design studies as this type of study is generally considered the strongest form of empirical evidence. Future studies should also be limited to patients with PD in order to determine the effects of botox injections among this population.

Further study of standardized procedures, botox injections compared with other treatments, long-term side-effects related to botox injections, and the lowest effective dose would serve to enhance the evidence for the use of botox as treatment for drooling associated with PD. The development of a best practice protocol for the use of botox as treatment for drooling among patients with PD would also be beneficial if this treatment is to be used clinically.

Conclusions

Based on the above critical analysis, botulinum toxin should be used in the treatment of drooling among patients with PD. Further research is needed to determine the most effective procedures to be used in a clinical setting.

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