Critical Review: The Effectiveness of Botulinum Toxin in the Treatment of Children with Drooling Problems

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This critical review examined the effectiveness of Botulinum toxin type A (BT) injections in the treatment of drooling problems in children with various neurological conditions. Study designs reviewed included: case study, case series, cohort study and controlled clinical trial. Overall, research supports the use of BT in the treatment of children who have cerebral palsy (CP) and who drool, however there was limited evidence to support its use with children who have a variety of other neurological disorders. Evidence was inconclusive regarding identification of the optimal site of injection and the optimal dosage of injection.

Introduction

Drooling or sialorrhea is a major problem for many children with neurological conditions, such as CP and developmental delay (DD) (Ellies et al., 2002). The act of drooling can have serious medical and social consequences on children. Medically, children may experience skin excoriation and breakdown, yeast infections, salivary aspiration, and/or dehydration (Suskind et al., 2002). Socially, children may be isolated and stigmatized by peers due to the unattractiveness of drooling (Crysdale et al., 2006). Also, caretakers may become frustrated with the constant need to replace bibs and clothes on a daily basis (Suskind et al., 2002).

Currently in the area of saliva management, no treatment provides optimal results. Treatment approaches that focus on behaviour modification and oral motor therapy do not have many studies to validate their efficacy. Therapy is very intensive and results have not been proven to be long lasting (Brei, 2003). Medications used to treat sialorrhea are associated with many adverse effects, including dry mouth with thick secretions, behaviour changes, urinary retention and constipation (Brei, 2003). Finally, there is a small body of research evidence that suggests surgical procedures are successful in reducing drooling, however complications associated with surgery are worrisome and include increased dental carries, gingival problems, post-op cysts and fistulas, edema and otitis media (Brei, 2003).

More recent studies have evaluated the effectiveness of using BT to treat drooling in adults with Parkinson's Disease and amyotrophic lateral sclerosis and children with neurological conditions. BT injections may be a safe way to decrease the amount of drooling with minimal side-effects and reversible results (Bothwell et al., 2002). BT is injected bilaterally into the submandibular (SMG) and/or parotid (PG) glands at various doses, usually under ultrasound guidance. BT binds to a cytoplasmic protein involved in the fusion of synaptic vesicles with the presynaptic membrane (SNAP-25). This process disrupts the secretory pathway for acetylcholine and causes chemodenervation (Jongerius et al., 2001). The release of acetylcholine is blocked and this prevents the secretion of saliva. Eventually the axons re-sprout and new acetylcholine receptors are formed (Savarese et. al., 2004). A review of the available literature is warranted to determine if this is a viable treatment option for the management of drooling in children with various neurological conditions.

Objectives

The primary objective of this paper is to critically evaluate existing literature regarding the effectiveness of BT as treatment for children with various neurological conditions who drool. The secondary objective is to propose evidence-based practice recommendation regarding the use of BT for children with neurological conditions.

Methods

Search Strategy

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

> (drooling) OR (sialorrhea) AND (botulinum toxin type A) OR (botox) AND (children) OR (child).

The search was limited to articles written in English.

Selection Criteria

Studies selected for inclusion in this critical review paper were required to investigate the impact of BT injections to treat drooling in children with neurological conditions. No limits were set on the demographics of research participants or outcome measures.

Data Collection

Results of the literature search yielded the following types of articles congruent with the aforementioned selection criteria: case study (1), case series (3), cohort study (2), and controlled clinical trial (1).

Results

Case Study:

Jongerius et al. (2005) evaluated the effects of BT to treat posterior drooling in a child with CP. The subject was injected with 25U of BT in *each* SMG using ultrasound guidance at two separate times. Measurement tools included salivary flow rate (mL/min) measured through weighing dental rolls that had been placed in the subject's mouth; the drooling quotient (DQ) expressed as a percent estimated from the ratio of observed drooling episodes and the total number of observations; drooling severity as measured by a visual analogue scale (VAS); the Teacher Drooling Scale (TDS) which rates drooling on a 5-point scale from constant (5) to none (1); and changes in clinical symptoms including congested breathing, swallowing difficulties, and aspiration associated with pneumonia. Measures were obtained before the injection, at 1, 8, 18, and 24 weeks after the first injection, and at 4, 8, 18, and 28 weeks after the second injection. Results indicated that salivary flow rate was reduced by 47% two weeks after the injection, the TDS decreased from 5 to 2 eight weeks after the first injection, the drooling quotient was reduced by 91.3%, and the VAS changed from 13 (severe) to 78 (mild). Posterior drooling improved and no side effects were reported.

The study included only one subject, thus results of the study cannot be generalized to the population of children with CP who drool. The authors do not discuss the reliability and validity of the measurement tools used in this study. In particular, using dental rolls to measure saliva is not the gold standard when measuring saliva volume. However, this method has been used in most of the studies to measure saliva volume with this population. The gold standard is cannulation of the salivary ducts, however this method has limitations when applying it to the clinical setting (Suskind et. al., 2002). Measurements of saliva flow rate were always conducted at the same time and multiple times (two times per day), making the measurements more reliable. Salivary flow rates were always conducted by the same SLP, thus the results may be more reliable verses having more than one SLP obtain measurements. Experimenter bias may have occurred because individuals collecting measurements were not blinded. Results were analyzed by looking at the numerical values verses using statistical analysis. This was appropriate due to small sample size. Finally, the researchers did not outline what a significant reduction in saliva was in terms of DQ, VAS and TDS.

Case Series:

Bothwell et al. (2002) assessed the effectiveness of BT in the treatment of excessive drooling in 9 children with CP and other neurological deficits. Using a strict aseptic technique to locate the superficial portion of the PG, a single injection of 5U of BT was made into *each* PG. Measurement tools included rating scales for severity and frequency of drooling, quantity of drooling by weighing dental bibs after 5-10 minutes of wear, DQ, and caregiver records documenting changes in the site of injection or health of the subject. Measurements were obtained at baseline, 2 and 4 weeks post-injection, and then once every 4 weeks until return to baseline measurements or until 16 weeks post-injection. Results indicated that successful outcomes occurred in 5 of the 9 patients based on a set of pre-determined criteria. The only side effect observed was that one participant experienced a temporary increase in saliva production. The authors concluded that BT is a relatively effective treatment for some children.

Jongerius et al. (2001) evaluated the effectiveness of BT injections in children with CP who drool. Using ultrasound guidance, BT was injected into *each* of the SMG over 2 sites with a dose dependent on the child's weight (30U <= 15kg, 40U 15-25kg, 50U >25kg). Measurement tools included a drooling severity and frequency scale, saliva flow rate as measured using dental rolls, and a questionnaire to reflect QOL issues including drooling, eating, drinking and daily care. Measurements were obtained at baseline, 2, 4, 8, and 16 weeks after the injections, with the exception of the questionnaire which was filled out only before and after BT injections. Results demonstrated a reduction in salivary flow rate of 51-63%. The only side effect observed was mild thickening of saliva. The authors concluded that their results support the hypothesis that BT injections into the SMG decreases salivary flow rate.

Ellies et al. (2002) assessed the effectiveness of BT in the treatment of drooling in 5 neurologically disabled children. Through ultrasound guidance, *each* PG was injected with 22.5U of BT fractionated into 3 doses of 7.5U (with the exception of 1 participant who received 15U in each) and *each* SMG received one injection of 10U. Measurement tools included

dental rolls to obtain salivary flow rate. Measurements were taken at baseline, and weeks 1, 2, 4, 8 and 12. Results demonstrated that 3 participants reported a distinct improvement of symptoms within the first week and 2 reported an improvement within the first 2 weeks. There was a sharp drop in salivary flow rates beginning within the first week, however after 12 weeks rates approached pre-treatment levels. The authors concluded that BT injections significantly reduced salivary flow rates in all patients studied. No side effects were observed.

In the case series studies conducted by Bothwell et al. (2002), Jongerius et al. (2001) and Ellies et al. (2002), the authors did not describe where patients were recruited from or provide a list inclusion and exclusion criteria. Also, they did not describe the participants in detail. They only provided the age and diagnosis of each participant. Aside from the study conducted by Bothwell et al. (2002), the participants are not a homogenous group, as many of them have different neurological disorders. BT may be more effective in treating drooling in one neurological disease verses another. All of the study results may have been affected by participant selection bias, performance bias and experimenter bias. The small sample size in each of the studies did not allow results to be generalized to similar populations. The authors did not outline a pre-determined set of criteria to define "successful treatment." As mentioned previously, the reliability and validity of measurement tools used were not discussed and are unknown. Finally, the authors appropriately interpreted the results without using statistics due to the small sample size.

Cohort Studies:

Savarese et al. (2004) evaluated the effects of BT when injected into the PG of children with CP and severe intermittent drooling. An electromyographic needle was used to inject *each* parotid gland with 10U and 5U at two different sites in 21 subjects. Measurement tools included a VAS to measure severity and frequency of drooling, the number of bibs per day, dental rolls to measure salivary secretion and a post-injection questionnaire. Measures were obtained at the initial visit (baseline), 1, 3, and 6 months post-injection, in addition to a telephone follow-up at 2 weeks and 2 months to obtain severity and frequency measures. Results were analyzed using four one-way within subject ANOVA. The results demonstrated a significant reduction in the frequency ($p<.05$) and severity ($p<.05$) of drooling, saliva production ($p<.05$) and number of bibs used ($p<.05$) with a large effect size associated with intervention. Also, the post injection questionnaire revealed that 53% of respondents reported a marked improvement and 21% reported moderate improvement. There were no reports of adverse reactions to BT.

The study was an open label study; therefore health providers and subjects were aware of the treatment given. This may have led to experimenter bias and performance bias. The sample size included 21 participants, which seems to be a reasonable number. There was no mention of a power analysis to determine the optimal number of participants needed to ensure a significant difference really exists when statistical analyses are performed. A list of inclusion and exclusion criteria was used to select subjects and to ensure participants shared similar characteristics. However, the researchers did not describe where participants were recruited from and they did not select subjects randomly which may have led to participant selection bias. All subjects had CP and were not receiving treatment for sialorrhea. By controlling for these factors, the researchers were able to say with more certainty that reduction in saliva flow was due to BT verses other forms of treatment. The study used 2 objective measures to investigate effects of BT on saliva production (# bibs & dental rolls). To ensure accuracy of measurement of salivary secretion (dental rolls), the time of day and position of the child during the objective analysis were kept constant. As mentioned previously, the reliability and validity of the measurement tools used are not known. To ensure correct placement of the BT, an electromyographic needle was used. Placement of injections may have been more accurate if ultrasound guidance had been used. During the course of the study there were 2 patients lost to follow-up. The authors did not say whether these patients were included in the statistical analysis. If they were not, this may have altered the results of the study. The authors used four one-way, within subjects, ANOVA correctly and included summary statistics for Wilks' A, F statistics, p values and multivariate effect sizes.

Suskind et al. (2002) evaluated the safety and efficacy of intraglandular BT injections in the treatment of sialorrhea in children with CP and brain injury. Twenty-two subjects were broken into 2 groups. Group one consisted of 12 subjects who received SMG injections at different dosages (10U, 20U & 30U). Group two consisted of 10 subjects who received SMG and PG injections in different dosages (30U SMG & either 20U, 30U or 40U PG). Injections were performed using ultrasound guidance. Measurement tools included the "drool rating scale" which included quality of life (QOL), physical, and caregiver issues and DQ. The authors attempted to

use dental rolls to measure amount of saliva, however they experienced difficulty carrying out the procedure with this particular sample of subjects. Measurements were obtained at the screening, baseline, and 1, 2, 4, and 8 weeks post-injection. Results demonstrated that group 2 (SMG + PG) appeared to respond more, at 80%, than group 1 (SMG), at 33%. There were significantly more non-responders in group 1 verses group 2. A t-test was performed to evaluate changes in the drooling rating scale. Significant changes were found in the physical and caregiver portions of the "drooling questionnaire" verses QOL. No side effects were observed.

The study was an open-label study, therefore experimenter and performance bias may have occurred. Subjects were chosen based on inclusion & exclusion criteria to ensure they controlled for effects of other treatments for sialorrhea. Subjects were not randomly chosen which may have led to participant selection bias. Twenty-two subjects took part in the research study, which appears to be adequate. Of the 22 subjects, 5 of them were "recycled" which may affect results of the study. Participants were divided between 2 groups, but researchers did not match the subjects between groups based on age, gender, etc. As mentioned previously, reliability and validity of measurement tools are unknown, however the authors discussed difficulties in measuring saliva volume. Ultrasound guidance was used when injecting BT into the SMG and the body of the PG, but not when injecting the tail of the PG. Accuracy of needle placement can only be assured for the injections where ultrasound guidance was used. A student t-test was conducted to measure changes in post-injection ratings of the questionnaire. All participants were combined as 1 group because of the small sample size which was appropriate. Finally, the authors used parametric statistics on a rating scale (ordinal data), which is not ideal.

Controlled Clinical Trial:

Jongerius et al. (2004) examined the effects of scopolamine verses BT in the treatment drooling in 45 children with CP. Participants used a scopolamine patch for 10 days followed by a wash out period of 2 to 4 weeks. Through ultrasound guidance, a single injection of BT was fractionated and divided over at least 3 sites to *each* SMG with the dosage determined by the weight of the subject (15U/SMG < 15kg, 20U/SMG 15-25kg, 25U/SMG >25kg). Measurement tools included the DQ, VAS and TDS. Parents were asked to document all possible effects of BT in a diary. The DQ and VAS were measured at baseline, day 10 of scopolamine, and 2, 4, 8, 16 and 24 weeks after BT. The TDS was measured at baseline and after BT at 8 and 24 weeks. Results of 39 participants were analyzed using MANOVA of repeated measurements to identify patterns of response over time, paired t-tests to analyze differences of paired observations of the DQ and VAS at subsequent measurements, a frequency analysis to determine the percent of responders in the population, and a Wilcoxon signed ranks test to analyze change in the TDS (an ordinal scale). Results found that compared to baseline, drooling was reduced during scopolamine and BT, and that drooling during the two forms of treatment did not differ significantly. Successful treatment with BT occurred in 61.5% of participants as defined by a 2-point decrease on the TDS. Moderate to severe side-effects occurred in 71.1% of subjects using scopolamine, whereas BT was associated with non-severe, incidental adverse effects.

Participant selection bias may have occurred, as participants were not chosen randomly. They were chosen consecutively from a particular clinic. The study had clearly defined inclusion and exclusion criteria to ensure participants were not receiving any other treatment for drooling management and that all participants had a shared diagnosis of CP. The study was open-labeled; therefore performance bias may have occurred. An independent employee assessed the primary outcome parameters and was blinded for the status of the participating patients, which increases the reliability of the results. Participants acted as their own controls by receiving scopolamine first followed by a washout period and then BT injections. The researchers used multiple measures to determine the effects of treatment, thus if both measures demonstrated significant reductions in drooling, it would be more probable that results were actually true. The researchers conducted a power analysis before the study began to determine the number of participants needed to obtain a power of 80% with an alpha of .05. They needed 40 participants, so they recruited 45 to account for potential drop-outs. The researchers reported all drop-outs and adjusted the data to account for missing data by (1) carrying the last observation forward, and (2) using a worst-case scenario (WCS) system where all missing data was replaced by baseline values so the effect difference between the therapies was "reduced" by introducing a bias toward the null. The researchers compared the results of both of these approaches. The authors clearly defined what "significant results" were before the start of the study and used appropriate statistical tests. The researchers used a Wilcoxon signed ranks test to analyze ordinal data of the TDS and MANOVA and paired t-tests to analyze interval and ratio data.

Recommendations

Based on the available research that evaluates the use of BT to treat children with drooling problems, the literature demonstrates that BT is an effective treatment for drooling in children with CP. There is less evidence to support its use with other neurologically impaired children. The available evidence suggests that BT helps to reduce the amount of drooling in this population with minimal side effects, unlike the use of pharmacological drugs such as scopolamine. Also, treatment is reversible, thus it may be preferred to surgical intervention.

Several concerns regarding the design and methodologies of the studies exist. These concerns include; small sample size for several of the studies, participant selection bias, performance bias, experimenter bias and unknown reliability of the measurement tools, namely the use of dental rolls to measure saliva volume. Due to these design and methodological flaws, clinicians and other health care professionals who provide this treatment option should be cautious when deciding to use BT to treat children with drooling problems. Children should be monitored closely to ensure adverse reactions do not exist as each child may react differently to the BT injections.

Further research is needed to clarify and confirm the research that has already been completed. Future research should focus on the following:

1) Include larger sample sizes to confirm the research that has already been completed and ensure results can be generalized.
2) Identify the optimal dosage and site (SMG and/or PG) to inject BT.
3) Compare the effectiveness of BT injections to other available interventions to treat drooling in children, such as medication, surgery and oral motor exercises.
4) Evaluate the long-term effects of BT to see if any long-term adverse effects exist.

Conclusions

In conclusion, this literature review provides speech language pathologists with a greater understanding of the effectiveness of BT injections in the treatment of drooling problems in children with neurological conditions. It appears that BT injections are effective in reducing drooling in children with CP with minimal side effects. Further research, such as large sample studies of optimal dosage and site of injection should lead to more refined evidence of the effectiveness of BT injections for treatment of drooling problems in children with CP. Speech-language pathologists should be able to make more informed decisions regarding incorporating BT injections into their treatment practices.

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