Critical Review:
The effectiveness of botulinum toxin A injections for improving pharyngoesophageal spasm following laryngectomy to allow for the acquisition of tracheoesophageal voice

Christina Senchuk
M.Cl.Sc (SLP) Candidate
University of Western Ontario: School of Communication Sciences and Disorders

This critical review examines the effectiveness of Botulinum toxin A (BtA) injections for improving pharyngoesophageal (PE) spasm following laryngectomy to allow for the acquisition of tracheoesophageal (TE) voice. Study designs include: pre-test post-test controlled designs, retrospective case series pre-test post-test designs and a single subject case report. Overall, the research supports the use of BtA as an effective method for improving PE spasm; however, results are variable and dependent on a number of factors including injection technique, injection site, degree of fibrosis, and dosage amount.

Introduction

Tracheoesophageal (TE) voice post laryngectomy is the only method of alaryngeal voice that allows the patient to use pulmonary air in order to support a voice that is more natural sounding and allows for greater intensity of the speech signal (Doyle & Keith, 2005). TE voice requires air to be taken in through a stoma into the lungs and exhaled through a one way valve voice prosthesis situated in a fistula connecting the upper posterior tracheal wall and the anterior esophageal lumen. The air is then diverted up into the esophagus causing the pharyngoesophageal (PE) segment to act as a vibrating source and produce voice (Hoffman, Fischer, VanDenmark, Peterson & McCulloch, 1997). Failure of the PE segment to adequately vibrate, and thus inhibit the acquisition of TE or esophageal voice, can be caused by numerous factors including recurrent tumour, scarring, pharyngeal stenosis, pharyngeal stricture, or pharyngoesophageal (PE) spasm (Chao, Graham & Hoffman, 2004).

PE spasm (or pharyngeal constrictor hypertonicity) occurs when hypertonic muscles in the PE segment restrict the airflow through the esophagus limiting the vibration of the PE segment which subsequently results in TE voice failure (Chao et al., 2004). Treatments for PE spasm have been utilized such as cricopharyngeal myotomy and pharyngeal plexus neurectomy; however, these procedures carry surgical risks and complications, including the requirement of anesthesia that might not be tolerated by the patient, are costly, and have not been documented to be consistently effective (Hoffman et al., 1997).

A body of literature has emerged to document the efficacy of Botulinum toxin A (BtA) injections for relieving PE spasm. These injections cause a localized muscle paralysis or paresis by blocking the presynaptic release of acetylcholine at the neuromuscular junction, therefore relaxing the muscles and allowing for improved vibration of the PE segment (Zormeier, Meleca, Simpson, Dworkin, Klein, et al., 1999). The use of BtA, if successful, can allow for a more cost effective and safer alternative in eliminating PE spasm excluding the need for further surgical risks and complications, such as anesthesia, associated with other forms of treatment (Ramachandran, Arunachalam, Herrun, Marsh & Samuel, 2003).

Objectives

The primary objective of this paper is to critically evaluate the existing literature regarding the effectiveness of BtA injections for improving PE spasm following laryngectomy to subsequently allow for the acquisition of TE voice. The secondary objective is to propose evidence-based practice recommendations regarding the use of BtA for PE spasm.

Methods

Search Strategy

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

(tracheoesophageal) AND (botox) AND (spasm) OR (TEP) AND (botox) OR (tracheoesophageal) AND (pharyngoesophageal spasm)

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 BtA in PE spasm following laryngectomy to allow for the acquisition of TE voice. 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: single group pre-test post-test controlled designs (5), retrospective case series pre-test post-test designs (3) and a single subject case report (1).

Results

Single group pre-test post-test controlled designs

Blizer, Komisar, Baredes, Brin & Stewart (1995) evaluated the effectiveness of Botulinum toxin A injections for cricopharyngeus muscle spasm in patients following laryngectomy who were unable to acquire rehabilitation of speech with a tracheoesophageal puncture. Six male laryngectomized patients (ranging from 55-77 years old) participated. Two patients were chosen for treatment after undergoing a myotomy and demonstrating no speech improvement, 2 were chosen for therapeutic and diagnostic indications that were not mentioned and the remaining 2 were chosen because their medical conditions did not allow them to participate in surgical interventions. Patients completed a pretreatment rating which was represented as a percentage. They were each injected at three sites on each side of the midline and the effective dose ranged from 15 to 45 units (30 units on average) of BtA. Patients returned a week following their initial injection and positive effects were noted in all patients based on patient ratings with an average of 40% improvement (with a range of 20%-60%). The effects were reported over an average of 12 weeks (range 10-20 weeks).

Crary and Glowasky (1996) evaluated eight patients post laryngectomy to establish whether the use of Botulinum toxin A was an effective method in reducing pharyngoesophageal (PE) spasm and subsequently improving voice and swallowing function. Six men and two women with a mean age of 65 years (range, 55-77) participated, 4 of which presented with only swallowing impairments and 4 with both swallowing and voice impairments. Patients underwent videoflouroscopic assessment and lidocaine hydrochloride was injected into the area of maximal PES narrowing in all patients. If a speech and/or swallowing function was judged by the patient as improved the impairment was concluded to be a spasm and not a stricture, and BtA injections were subsequently given. Between 2.5 U- 25U of BtA solution was injected into 4 patients who presented with PE spasm alone (3 male and 1 female). All 4 patients reported improved swallowing and/or voice function. The duration of benefit was measured in 3 patients who received multiple injections. Those patients injected with larger doses (25 U) resulted in a duration benefit that was 7 months or longer compared to those injected with 2.5 U sustaining a duration benefit of 2 weeks to 1 month post injection. Fluoroscopopy objectively measured maximum pharyngoesophageal segment opening and results indicated that a larger dose resulted in greater PES opening; however, one patient indicated improvement in swallowing functioning although there was no visible increase in the opening of the PES after an injection of 2.5 U. Speed of bolus transit was measured and results indicated that an injection of 25 U of BtA resulted in a 25% decrease in bolus transit time. Crary and Glowasky (1996) concluded that BtA was an effective method in alleviating PE spasm improving TE voice and swallowing function.

Lewin, Bishop-Leone, Forman & Diaz (2001) evaluated the use of Botulinum toxin A in relieving pharyngeal constrictor hypertonicity in order to acquire tracheoesophageal speech following laryngectomy. Specific outcome measures included data regarding vocal outcome, duration of effect, and need for reinjection to maintain long lasting TE voice. Twenty-three laryngectomized patients (19 men and 4 women) between the ages of 37 and 83 participated and we identified as having PE spasm through tracheoesophageal insufflation testing. The ability to produce fluent speech pre-test was assessed and defined as “an ability to produce 10-15 syllables per breath and sustain a vowel production of /a/ for a minimum of 10 seconds at interesophageal pressure levels less than or equal to 20 mmHg on a pressure manometer” (Lewin et al., 2001). Two to three Botulinum toxin injections (a concentration of 50 mouse units per cc of normal saline) were inserted with a Teflon EMG-guided needle lateral to the stoma between markers that were placed during videoflouoscopic recording. Results indicated that 20 participants were successful in achieving TE voice following BtA injection. Two of the remaining unsuccessful participants refused a second injection and 1 participant was unsuccessful after 3 BtA injections and experienced gradual decline in her speech due to the reoccurrence of constrictor hypertonicity. Fifteen participants were successful at acquiring TE voice after only 1 injection and 4 were successful after 2 injections. The remaining participant failed to achieve criteria for fluent speech. He was able to acquire TE voice although it was effortful and tight. The average duration of effect was 20.4 months (range 5-37 months). Lewin et al. (2001) concluded that BtA injections are an effective method of reliving PE spasm to acquire TE voice.

Ramanchandran et al. (2003) considered the effects of Botulinum toxin A on patients following laryngectomy who did not develop useful tracheoesophageal voice or who developed hypertonic voices post laryngectomy and were suspected of the presence of pharyngoesophageal muscle spasm. This study examined 10 patients (9 male and 1 female) with an average age of 58 (range, 48-71 years). Four patients

underwent a myotomy that was proven to be unsuccessful in restoring TE voice. All patients underwent videofluoroscopy to confirm the presence of a pharyngoesophageal spasm. Patients were injected transcutaneously with 10 mL of 1% lidocaine, a form or anesthetic, into the muscle spasm as a pre-screen to identify if they would benefit from BtA injection. The patients attempted to voice and if the spasm subsided and allowed air to pass through the esophagus it was thought that the patient would benefit from BtA. All patients were injected with 500 Units of BtA which was dissolved in 1-6 mL of saline solution. The Sunderland Surgical Voice Restoration (SVR) voice rating scale was utilized to allow the patients to assess qualitatively their voice quality both pre- and post-treatment. The rating indicated +5 for severe hypertonicity, 0 indicating optimal tonicity and -5 indicating severe hypotonicity. Results indicated that a conversational level of TEP voice was achieved in the seven patients that originally presented with no voice. Of those patients who represented with hypertonic voice 2 indicated improvement on the SVR scale (+4 to +1 and +3 to +2 respectively). The one female patient reported the voice converting to a hypotonic voice (+2) that she reported she did not care for. Her voice was reverted back to her former hypertonic voice within 4 months. Five patients only required one injection and were satisfied with their voices. Four patients required additional injections to maintain the optimal tonicity to their voice (One patient required 6 injections, two patients required 3 injections, and one patient required 2 injections). These injections ranged from 2-17 months. Ramanchandran et al. (2003) concluded that BtA injections are beneficial for eliminating PE spasm in patients following laryngectomy.

Zormeier et al. (1999) examined patients following laryngectomy with pharyngoesophageal spasm and evaluated, both quantitatively and qualitatively, the effects of BtA injection on the patients' tracheoesophageal voice quality. Eight male patients participated with a mean age was 61 years (ranging from 42-78). Four patients had undergone previous myotomy. PE spasm was evaluated based on clinical symptoms, pre-TEP insufflation pressures, tracheal back pressure measurements, and Barium swallow evaluation. Botulinum toxin A was given through the anterior neck skin, in the midline and the inferior portion of the bulging posterior pharyngeal wall as identified through fluoroscopy and 60-90 units were given (20-30 units at each of the 3 sites). Outcome measures included acoustical measures, subjective ratings by the speaker, and perceptual rating by 3 trained listener judges using a seven-point equal-appearing interval scale. All measures were recorded pre- and post-BtA injections. Results indicated that all patients reported improved voice quality. Intrajudge and interjudge reliability reached the 95% confidence level and self rating tended to correlate highly with trained listeners. The judges rated 7/8 of the patients with improved voice after injection and 5/8 were rated in the good-excellent range. The one patient who was not rated to have an improvement had a bilateral hypoglossal nerve injury; although his perception of his own voice was evaluated to be improved. Tracheal air pressure measurements revealed that 6 of 8 patients demonstrated normal pressures after injection. Zormeier et al. (1999) concluded that BtA is an effective and reliable method of alleviating PE spasm following laryngectomy.

Retrospective case series pre-test post-test designs

Hamaker and Blom (2003) evaluated the use of BtA injections in 62 patients following laryngectomy who were unable to successfully acquire tracheoesophageal speech between 1991 and 2002. All patients underwent air insufflation testing and were established to have pharyngeal constrictor (PC) muscle spasm. Patents were injected unilaterally at multiple sites with 100 units of BtA diluted in 3mL of saline under EMG guidance into the contracted pharyngeal constrictor muscles. All patients were divided into three groups after injection. Group I patients all had fluent voices and complete PC muscle relaxation with intratracheal phonation pressure of 20 to 40 cm H_2O and the ability to say 15 to 20 uninterrupted syllables. Group II patients presented with strained voices and incomplete PC muscle relaxation with intratracheal phonation pressure of 45 to 70 cm H_2O and the ability to say 7 or 8 uninterrupted syllables. Group III patients presented with either severely limited voice or were aphonic. Patents were telephoned 72 hours after the injection to assess if the BtA injection had taken effect. They were reassessed 2 weeks later for phonatory duration and intratracheal phonation pressure. Results indicated that after 1 BtA injection, 49 patients were classified in either group I (41) or group II (8) and 34 of these patients maintained TE voice for more than 6 months, Group 1 (28) or Group II (6) respectively. Fourteen of the 49 only responded with relaxation lasting between 6 to 12 months. Out of 13 failures, 6 were able to move into group I after a second BtA injection. Forty-one patients maintained relaxation of the PE spasm and required no further treatment after a second or third injection. Myotomies were performed for 8 patients who did not benefit from a second or third Botox injection. The myotomies resulted in 6 patients with fluent speech, one who did not benefit but subsequently benefited form a third BtA injection after the myotomy, and one patient who BtA produce a hypertonic voice and he requested no further BtA treatment. Hamaker and Blom (2003) concluded that PE spasm could be successfully

eliminated with the administration of BtA post laryngectomy.

Hoffman et al. (1997) sought to evaluate the effectiveness of Botulinum toxin A in PE spasm in patients who failed to acquire TE voice or presented with strained or intermittent speech following a total laryngectomy between 1991 and 1994. The patients selected presented with hypopharyngeal muscle tonicity as evident in difficulty phonating and were considered poor anaesthetic risks or had previously undergone myotomy that was unsuccessful. All patients were given a local trial of anaesthetic to evaluate whether inducing paresis of the hypopharyngeal muscles would improve their phonation. Analysis was performed on 8 patients (7 males and 1 female) with an average age of 60 years old (range, 39-76). One patient presented with a hypoglossal nerve paralysis and the injection was given on the ipsilateral side of the injured nerve in order to decrease the chance of morbidity from local diffusion of the BtA. Injections were given unilaterally and at 3 sites: superiorly at the junction between the base of the tongue and the middle constrictor muscle, inferiorly at the lower pharyngoesophageal segment, and at a site in the middle between the two points. The BtA injection took place with a Teflon EMG needle and initially 5 units in 0.2 ML of saline was injected at each site. In 1992 a standardized injection protocol was set in place increasing the initial dosage of BtA to 45 units total (15 units at each site). Results indicated that 5 patients required repeated injections (ranging from 2-108 weeks) and were primarily those in the initial group who only received 15 units of BtA initially. The amount of air pressure needed to produce TE speech and phonation was recorded in 6 of the 8 patient's pre- treatment. Improved TE speech after injection was noted in 7 of the 8 patients. Five of the seven were documented as having "major voice improvements". Two patients were categorized as "treatment failures". One was due to the closure of the TEP after which he decided to employ an electrolarynx and the other due to lack of improvement after BtA injection who developed an upper respiratory tract infection with poor voicing. The one patient who did not develop TE speech after injection was assessed pre-treatment to have relatively low phonation pressures. Hoffman et al. (1997) concluded that BtA injection for PE spasm is a safe and effective treatment for the acquisition of TE voice.

Krause, Hempel & Gurkov (2009) sought to evaluate retrospectively the efficacy of Botulinum toxin A on eliminating pharyngoesophageal spasm to improve poor tracheoesophageal voice quality. This study also sought to evaluate the efficacy of BtA on prolonging functional durability of voice prostheses in patients following laryngectomy between 2001 and 2007. Eleven patients (9 male and 2 female) with a mean age of 58 (range, 47-70 years) participated, 6 of whom had dysphagia. A PES spasm was identified in all patients through a radiographic swallow study. Between 80 to 200 units of BtA dissolved in 2.5 mL of saline was injected into the PES musculature in a 4-quadrant pattern into each participant during rigid pharyngoscopy while the participants were under general anesthesia. One participant, who refused anesthesia, was injected under electromyographic control. Participants received a total of 22 BtA treatments ranging from 1 to 7 treatments per patient. In addition, the 6 participants who complained of dysphagia received a stepwise bougie dilation using elastic gum bougies. Patient's voice quality was assessed quantitatively by dividing the patients into 3 subgroups according to the grouping in Hamaker and Blom (2003). Pre-injection, patients were evaluated a total of 33 times and presented as once in group I (15-20 uninterrupted syllables), 23 times in group II (7-8 uninterrupted syllables), and 9 times in group III (aphonic or 1-2 syllables). One week post-treatment voice quality was reassessed and the results indicated groupings improved to 13 times in group I, 19 times in group II, and once in group III. On 18 occasions symptom score improved by one level (from III to II or from II to I) In addition, subjective severity of symptoms was recorded by the patients and improvement of voice quality was reported in 94% of instances. Therapeutic success lasted for 4 to 77 weeks (a mean of 22 weeks). Those who reported dysphagia pre-treatment were injected with 14 BtA injections total and of these 3 times were reported mild, 4 times reported moderate, and 7 times were reported as severe. Only 1 of 14 treatments demonstrated a significant improvement of dysphagia. The life span of the prosthesis pre-treatment was 2 to 60 weeks (mean 12 weeks) and post-treatment it demonstrated a statistically significant increase ($p=.008$; Wilcoxon rank test) to 6 to 124 weeks (mean 34 weeks). Krause et al. (2009) concluded that BtA injections are a successful method in improving TE voice following laryngectomy as well as prolonging TE prosthesis durability; however, treatment was not successful in improving dysphagia.

Single subject case report

Terrel, Lewin & Esclamdo (1995) conducted a single subject case report to evaluate the effectiveness of Botulinum toxin A in relaxing a pharyngoesophageal muscle spasm in a 70-year old male following laryngectomy. The patient was fitted for a TE voice prosthesis and failed to acquire TE voice successfully. He then underwent a stoma revision myotomy; however, was still unable to acquire TE speech successfully. Pharyngeal constrictor hypertonicity was confirmed based on a reduction of intraesophageal pressures during insufflation testing and a Lidocaine

blockade was administered and improved speech abilities. The patient was then injected with 15 units of Botulinum toxin (7.5 units on each side of the midline) into the cricopharyngeous muscle with an 27-gauge Teflon-coated electromyography needle. The patient's speech fluency had reportedly improved to a minimum of 10 syllables per breath within 48 hours of the treatment. Intraesophageal peak pressures recorded had dropped to below 20mm Hg. The patient did not require additional BtA injections and was recorded as having confident TE speech for 9 months post-treatment.

Discussion

Overall, it appears that BtA injections are a safe and effective way in reducing PE spasm in order to acquire TE voice. However, inherent limitations may affect the reliability and validity of the studies and must be considered when taking into account the results. Many factors can limit the ability of the results to be generalized and should be considered in the analysis of the findings.

Subject selection

Many of the studies included a relatively small sample size with primarily male participants. Only three studies included more than 10 participants, Lewin et al. (2000) with 23 participants, Hamaker and Blom (2003) with 63 participants, and Krause et al. (2009) with 11 participants respectively. In addition, the number of female participants was grossly underrepresented. Female representation included 1 of 4 (Crary & Glowsy, 1996), 4 of 23 (Lewin et al., 2000), 1 of 10 (Ramachandran et al., 2003), 1 of 8 (Hoffman et al., 1997) and 2 of 11 (Terrell et al., 1995). Studies only including male participants included Blizer et al., (1995); Zormeier et al., (1999), and Terrell et al., (1995). Hamaker and Blom (2003) neglected to state the gender of any of the 62 participants in their study rendering the reader to question whether these findings are representative of both male and female patients post laryngectomy. Positive results were reported specifically for 1 female participant (Crary & Glowasky, 1996) and another 1 female (Hoffman et al., 1997). Female participants may have benefited from BtA in studies conducted by Lewin et al. (2000) and Krause et al. (2009) although it was not specifically stated if the females injected were the patients who benefited from BtA. Therefore, findings concerning generalization to other females post laryngectomy presenting with PE spasm should be interpreted with caution. A greater representation of female participants could allow for a better indication if BtA injections are beneficial for females under certain conditions and potentially give insight into which factors may influence the efficacy of BtA injections when comparing both male and female patients with PE spasm post laryngectomy.

BtA injection technique and injection site

A wide degree of variation exists in the aforementioned studies regarding injection technique, such as EMG guidance or videoflouroscopy, and site of injection. A standardized injection protocol was set in place in 1992, specifying injection at three sites on each side of the midline. Only 2 out of the 9 studies reported following this protocol (see Blizer et al., 1995. & Hoffman et al., 1997). Although they did not follow the specific protocol, Zormeier et al. (1999) injected at the anterior neck skin, in the midline and the inferior portion of the bulging posterior pharyngeal wall. Crary and Glowasky (1996) specified injecting at the narrowing of the esophageal lumen, Krause et al. (2009) in a 4-quadrant pattern, Terrel et al. (1995) on each side of the midline, and Lewin et al. (2000) at markers that were placed during videoflouroscopic assessment but were not clearly defined. The authors of two studies (Ramanchandran et al., 2003, Hamaker & Blom, 2003) did not specifically state the anatomical location of injected BtA limiting the ability to accurately replicate this study. Lack of consistency regarding BtA injection technique and site across studies provides difficulty in comparing the efficacy of BtA across participants. In addition, it provides difficulty in establishing whether differences in BtA efficacy are a result of injection technique, site, or potentially other unexplored factors.

BtA dosage

The previous studies have also demonstrated a wide range of dosages administered despite the established standardized injection protocol with the effective dose ranging from 15 to 45 units (30 units on average) of BtA. Two studies (Blizer et al., 1995 & Hoffman et al., 1997) reported using the standardized protocol resulting in all but 2 patents in the Hoffman et al. (1997) study reporting success. Varying doses have demonstrated to be effective for the majority of patients injected but not all. In studies done by Blizer et al. (1995), Crary and Glowasky (1996), Zormeier et al. (1999) and Terrel et al. (1995) all participants demonstrated some acquisition of TE voice. Only 3 of 23 patients (Lewin et al., 2000), 3 of 10 (Ramanchandran et al., 2003), 8 of 62 (Hamaker and Blom, 2003), and 2 of 8 (Hoffman et al., 2009) demonstrated no improvement in acquisition of TE voice post injection. In particular, exclusion of information regarding how many injections each individual patient received as well as the dosage received has significant implications on the studies completed by Krause et al. (2009) and Crary & Glowasky (1996) due to their inclusion of patients with dysphagia. Ninety-four percent of instances tested by Krause et al. (2009) demonstrated TE voice

improvement; however, dysphagia persisted in many patients. However, Crary and Glowsky (1996) found all patients reported improved voice and swallowing function. Results regarding the dosage administered and the effects on dysphagia could contribute to future research and a better understanding of the role BtA plays in dysphagia. There is evidence that increasing the initial dosage can result in longer lasting effects (Crary and Glowasky, 1996; Hoffman et al., 1997); however, this finding has not been irrefutably established. Although the majority of studies examined have varied their dosage amount of BtA injected, results have indicated that BtA is an effective method in reliving PE spasm to acquire TE voice.

Reinjection of BtA and duration of effect

Lidocaine, a form of anesthetic, was injected into the muscle spasm as a pre-screen in 4 studies to identify if the patients would benefit from BtA injection (Crary & Glowasky, 1996; Ramanchandran et al., 2003; Hoffman et al., 1997; Terrel et al., 1995). The patients attempted to voice and if the spasm subsided and allowed air to pass through the esophagus it was thought that the patient would benefit from BtA. The majority of patients who demonstrated improvement after the lidocaine screen subsequently demonstrated improvement in acquiring TE voice after the BtA injections. Future research could utilize this information as a step toward identifying which patients may positively benefit from BtA injections; however, further investigation is warranted.

Many patients were successful in acquiring TE voice after only 1 injection including all patients injected (Blizer et al, 1995; Terrel et al, 1995), 15 of 23 (Lewin et al., 2000), and 5 of 10 (Ramanchandran et al., 2003). After a second or third reinjection, the majority were able to acquire TE voice including 7 of 8 (Hoffman et al., 1997), 41 of 62 (Hamaker & Blom, 2003), 19 of 23 (Lewin et al., 2000) and 7 of 10 (Ramanchandran et al., 2003). Krause et al. (2009), Crary and Glowasky (1996), and Zormeier et al. (1999) failed to include the number of patients requiring reinjection or how many reinjections were administered.

Duration of effect was shown to vary from patient to patient with a range of 1-37 months for patients requiring re-injection. Zormeier et al. (1999) neglected to include the duration of effect.

Many patients were able to acquire and sustain TE voice with only one BtA injection and did not require a second injection. The authors were unclear as to why some patients obtain and sustain success after their initial injection while others do not. It is hypothesized that the neuromuscular junction is affected by the degree of radiation or surgical damage and prevents regeneration of acetylcholine receptor development sustaining the effect of BtA permanently (Hamaker & Blom, 2003). A focus for future research may be to evaluate important factors such as degree of radiation or surgical damage to the pharyngoesophageal musculature and establish under what conditions the PE spasm might optimally benefit from BtA injections in order to identify which patients may successfully benefit from this treatment.

Outcome measures

A large degree of variation exists in defining outcome measures in obtaining TE voice. Although successful patients were reported to have acquired TE voice, outcome measures were only evaluated both quantitatively and qualitatively in three studies. Zormeier et al. (1999) included acoustical measures (tracheal air pressure), subjective ratings by the speaker, and perceptual rating by 3 trained listener judges using a seven-point equal-appearing interval scale. Krause et al. (2009) evaluated patients by dividing them into groups of predetermined criteria including intratracheal phonation pressure and number of uninterrupted syllables as well as recorded the patient's subjective voice rating. Terrel et al. (1995) considered number of syllables per breath and intraesophageal peak pressures as well as patient's report of success. Four studies focused solely on quantitative measures including pharyngoesophageal segment opening (Crary & Glowasky, 1996), predetermined definition of successful TE voice acquisition (Lewin et al., 2000), phonatory duration, intertracheal pressure, and number of uninterrupted syllables (Hamaker & Blom, 2003), and phonation pressure (Hoffman et al., 1997). Two studies considered qualitative measures alone which included patient ratings (Blitzer et al., 1995; Ramanchandran et al., 2003). A significant limitation is evident in the wide array of outcome measures evaluating what specifically constitutes successful TE voice acquisition. This large diversity presents difficulty in comparing treatments across patients, injection techniques and dosages in order to determine which measures will identify optimal efficacy of BtA injections leading to TE voice acquisition.

Experimental design

It would be unethical to administer BtA to a healthy individual serving as control who does not show signs of PE spasm. Therefore, the patients in the aforementioned studies must serve as their own controls which results in the design of 8 studies yielding a level 3 in terms of level of evidence and 1 study a level 4 (Terrel et al., 1995) in terms of level of evidence. Given the inherent limitations of the study designs, the overall validity of the previously described studies would be described as suggestive in that BtA injections have shown to be an effective treatment in improving PE spasm for many individuals, although not all, and

subsequently allowing the acquisition of TE voice in patients following laryngectomy.

Recommendations

There is a sufficient body of evidence supporting that BtA injections are a safe and effective way to alleviate PE spasm in order to acquire TE voice for many patients; however, not all. It is recommended that further research on this topic be completed in order to more thoroughly analyze which variables may have an impact on the efficacy of BtA injections on PE spasm in order to acquire TE voice.

In order to improve on the evidence presented by the existing literature, future research in this area is encouraged to:

1. Utilize adequate sample sizes and the inclusion of more female participants.
2. Utilize the standardized injection protocol initially exposing participants to the same injection site, injection technique and dosage.
3. Focus on outcome measures that are both qualitative and qualitative in nature to allow for a more holistic evaluation of whether TE voice has been successfully acquired.
4. Consider additional variables such as degree of fibrosis, type of radiation, pre-treatment phonation pressure and stage of carcinoma. Researching whether these variables play a role in how effective the BtA injections are can lead to a better understanding and screening process in identifying patients who may optimally benefit from BtA injections in order to alleviate PE spasm and successfully acquire TE voice.

Clinical Implications

Despite the aforementioned limitations of these studies, the evidence presented here indicates that BtA injections are a successful way of alleviating PE spasm and acquiring TE speech. However, this result has been shown to be effective predominately for male patients. It is essential for speech-language pathologists to be sensitive to the less explored outcomes experienced by female patients and to observe potential variables that can impact a female from acquiring TE speech. In addition, based on the findings by Blitzer et al. (1995) and Hoffman et al. (1997) clinicians are encouraged to use the standardized injection protocol in order to facilitate TE speech acquisition.

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