Injection of botulinum toxin for the treatment of post-laryngectomy pharyngoesophageal spasm-related disorders

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ABSTRACT

INTRODUCTION Pharyngoesophageal spasm (PES) can cause dysphagia, central valve leak (CVL), and dysphonia in post-laryngectomy patients. Botulinum toxin has been used effectively for the treatment of PES, but data regarding patient-reported outcomes and efficacy for CVL are limited. We evaluated the results of botox injection for PES spasm using subjective and objective measures.

METHODS Data were collected prospectively (February 2010 to August 2013) on 13 patients undergoing botox injection for PES as identified by video fluoroscopy. We collected digital voice recordings, air-pressure measurements (APMs) for speech, and quality of life (QoL) data before and after the procedure: University of Washington QoL questionnaire (UW-QoL), MD Anderson Swallowing Inventory (MDADI) and the Voice Handicap Index (VHI-30).

RESULTS APMs for a sustained vowel decreased by 18% after botox injection, whereas maximum phonatory times increased by 63% (mean increase, 8 to 13 seconds). Sustained vowel amplitude decreased (mean, 87db to 83db) with an associated reduction in sustained vowel frequency (117Hz to 77Hz). MDADI scores improved by 10.2% overall, and UW-QoL scores showed an improvement in score of 7.6%. Mean scores for VHI-30 deteriorated by 2% overall but, when considering only those patients experiencing dysphonia, an improvement of 9.4% was seen. There was an overall net reduction for the CVL cohort of 12 speech valves in the year after injection.

CONCLUSIONS Our series confirm the safety and objective efficacy of botox injection for PES. QoL measurements were less convincing, and this disparity between subjective and objective measurements must be considered when treating such patients.

KEYWORDS

Botulinum toxin – Pharyngoesophageal spasm – Pharyngoesophageal hypertonicity

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Pharyngoesophageal segment (PES) hypertonicity and spasm is a well-recognised phenomenon in laryngectomees, and a frequent cause of dysphagia and/or dysphonia in such patients.¹ In addition to disrupting the physiology of swallowing, failure of PES relaxation prevents adequate airflow through the pharynx, and necessitates higher intra-tracheal phonation pressures,¹ which manifests as strained, spasmodic speech.² In those with a trans-oesophageal fistula (ToF) and speech valve, PES hypertonicity is the most common cause of trans-oesophageal speech failure,³ reportedly causing up to 79% of failures of trans-oesophageal voice.⁴ Recently, PES spasm has been implicated to cause central valve leakage (CVL) in ToF speech valves (whereby fluid leaks through the valve to cause the potential risk of aspiration).⁵

Traditionally, treatment for PES spasm is surgical myotomy, which is usually carried out at the time of laryngectomy and, less frequently, as a secondary procedure.

Efficacy is well documented, but there are potential complications and financial implications if surgical myotomy is undertaken as a secondary procedure.⁶

In recent years, use of botulinum toxin type-A injected into the PES to relieve hypertonicity has been advocated. This procedure can be carried out in the outpatient setting, and mitigates the potential complications of secondary surgical myotomy.⁷ In our practice, it is used primarily in patients who develop PES spasm even though a primary myotomy has been undertaken at laryngectomy. Botulinum is a potent neurotoxic agent that irreversibly prevents acetylcholine release at the neuromuscular junction, thereby reducing muscle tone. Its effects have been reported to commence within 72 hours and to last for ≈3 months.²

Several studies have evaluated objectively use of botulinum for PES spasm, and demonstrated its efficacy in the context of dysphonia and dysphagia.^{8,9} However, there is

a paucity of data relating to patient-reported outcome measures and treatment of PES spasm-induced CVL. We sought to evaluate objective and patient-perceived outcomes with respect to dysphagia, dysphonia and CVL.

Methods

Patients and setting

This was a prospective study carried out at Aintree University Hospitals NHS Foundation Trust (a multidisciplinary, tertiary, referral head-and-neck unit serving ≈2.5 million people within Merseyside and Cheshire, UK). Between February 2010 and August 2013, all post-laryngectomy patients followed up in the outpatient clinic with complaints of dysphagia, dysphonia and/or CVL in the absence of fungal infection or valve deterioration considered amenable to botulinum injection formed the study cohort. Patients with no demonstrable PES spasm at video fluoroscopy (VF) were excluded.

Procedure

Patients presenting with symptoms potentially resulting from PES spasm were screened initially using VF by speech and language therapists. Those patients in whom botulinum treatment was felt to be potentially beneficial (as determined by evidence of areas of spasm identified by VF in conjunction with symptoms of strained voice, CVL or dysphagia) were referred to a specialist clinic comprising a speech and language therapist, consultant radiologist, and consultant head and neck surgeon. During this referral, patients were re-screened and treated (if appropriate).

Patients first received an injection of 1% lidocaine (mean volume, 2 (range, 1–4) ml) under VF control using a 25G needle inserted via the transcutaneous route through the anterior neck into the area of identified spasm. Patients were re-screened after lidocaine injection to ensure that the observed region of spasm had relaxed because its anaesthetic effect reduces the spasm and contraction of muscle (which is detectable on VF). This method allows for further confirmation of the diagnosis before injection of botulinum (a more long-lasting and potentially toxic agent). After lidocaine administration, the syringe was removed and the needle left *in situ*: botulinum was administered through the same needle to ensure placement at the same site as the lidocaine. Five hundred-unit vials of Dysport® (*Clostridium botulinum* type-A) were reconstituted by dilution with physiological (0.9%) saline. In some cases, lidocaine and botulinum were injected at more than one site if multiple sites of spasm were identified on VF. In these cases, equal volumes of botulinum were injected into the areas of spasm identified. Mean dose per patient was 308 (range, 200–500) units.

Outcome measures

Objective measurements and patient-reported outcomes – as assessed using the University of Washington Quality of Life (UW-QoL) questionnaire,¹⁰ Voice Handicap Index-30¹¹ (VHI-30) and the MD Anderson Dysphagia Inventory (MDADI)¹² – were collected pre- and post-injection.

Patients completed the questionnaires during outpatient appointments. After injection, the mean interval to follow-up from time of procedure was 19 (range, 4–46) days. If appropriate, data were also collected to determine the number of valve changes required for each patient in the years before and after botulinum injection.

The VHI-30 comprises 30 questions and is scored from 0 to 120, with higher scores representing a higher degree of perceived voice disability. The MDADI comprises 20 statements related to dysphagia, and covers the global, emotional, functional and physical aspects related to swallowing. Patients choose one of five responses associated with a numerical score. A total score is calculated by summing all responses, calculating a mean value, and multiplying this value by 20 to give a total score out of 100,¹³ with a higher score representing a better swallowing outcome. The UW-QoL considers overall quality of life (QoL) in patients with cancers of the head and neck. It comprises single questions that address 12 domains and their impact on the patient in the preceding 7 days, and three general scores. Domains are scored on a scale from 0 (worst) to 100 (best) to give a composite score. The score used for the present study was the mean of the 12 domain scores out of a maximum score of 1,200 – higher scores indicate a better QoL.

Air-pressure measurements (APMs) in the trachea during speech were obtained using a Sunderland Air Pressure Meter™ (Sunderland Royal Hospital Innovation Team, Sunderland, UK). This is a sealed tracheostomal sphygmomanometer that gives pressure measurements in direct correlation with the amount of respiratory effort required to initiate airflow and sustain phonation, and hence reflect the underlying tone of the PES. APMs were taken during speech for each patient for free speech and sustained vowels. In addition, digital voice recordings of maximum phonatory time for a sustained vowel were undertaken on a Laryngograph Speech Studio™ (Laryngograph® Limited, London, UK).

Outcome data were reported by descriptive statistics because the small study cohort precluded more robust statistical analyses.

Results

Fifteen patients were referred to the specialist clinic during the study period. After re-screening, 13 patients were considered amenable to botulinum injection and included in the study. The 2 patients excluded were not eligible due to lack of evidence to support PES spasm on VF. Of the patients included, there was a male preponderance (11 males, 2 females). Mean age at injection was 67 (range, 54–80) years. Clinical characteristics of individual patients are depicted in Table 1.

All patients underwent uncomplicated procedures. Injections were well tolerated and side-effects were not observed.

APMs for a sustained vowel before and after the procedure were available for 8 patients, with mean pressures decreasing by 18% from 44cmH₂O before injection (range, 29–55cmH₂O) to 36cmH₂O after injection (range, 33–61cmH₂O). Maximum phonatory times for a sustained vowel were available for 6

Table 1 Clinical characteristics of the study cohort			
Age (years)	Sex	Voice type	Presenting symptom
69	M	Speech valve	CVL
54	M	Speech valve	CVL, voice
64	M	Speech valve	Voice
64	M	Speech valve	Voice
66	M	Speech valve	CVL
74	M	Speech valve	CVL
67	M	Speech valve	Voice
69	F	Speech valve	Voice, dysphagia
70	M	Speech valve	CVL
57	M	Oesophageal voice	Dysphagia
80	M	Oesophageal voice	Dysphagia
69	M	Speech valve	Voice, dysphagia
71	F	Speech valve	Voice, dysphagia
CVL = central valve leak			

patients, which increased from a mean of 8 seconds to 13 seconds; a 63% increase (range: pre-injection 1.9–15.8 seconds and post-injection 5.5–29.0 seconds). After botulinum injection, sustained vowel amplitude decreased from a mean of 87db pre-injection (range, 82–95db) to 83db post-injection (range, 76–88db), with an associated reduction in mean sustained vowel frequency from 117 (range, 57–175) Hz to 77 (range, 53–112) Hz.

Twelve UW-QoL and MDADI questionnaires were completed pre- and post-injection. The UW-QoL questionnaire showed an improvement post-injection of 7.6%, with a mean pre-injection value of 790 (range, 540–990) and post-injection value of 850 (range, 535–1190) (Fig 1). MDADI scores showed an improvement of 10.2%, with mean scores increasing from 49 to 54, respectively (Fig 2).

Eight patients completed the VHI-30. Mean scores before and after intervention were 51 (range, 38–87) and 52 (range, 21–80), respectively, a deterioration of 2.0% (Fig 3). However, when considering only those patients complaining of difficulty with voice, an improvement in score of 9.4% was observed, with mean scores decreasing from 64 to 58 (range: 18–87 pre-injection and 21–80 post-injection).

The requirement for speech-valve changes for CVL decreased markedly after botulinum injection, with the total number of valve changes per year for those complaining of CVL decreasing from 64 in the year preceding botulinum injection to 42 in the year after injection, a reduction of 34.4% (Figure 4).

Discussion

Principal findings of the present study suggest that botulinum injection is effective treatment for PES spasm in laryngectomees as evidenced by objective measures and patient-reported outcomes.

Figure 1 Scores for the University of Washington Quality of Life questionnaire for individual patients before and after botulinum injection

In confirming objective efficacy, these findings are in accordance with those reported previously.^{8,9} However, comparison between studies is impeded by the considerable variation in outcome measurements.^{14,15} The largest study to date – by Hamaker and Blom¹⁶ – used intra-tracheal phonation pressures in a similar manner to our study to assess outcomes in 62 patients. Tracheal APMs are considered to correlate closely with the effort required to produce trans-oesophageal speech. Therefore, reduction in APMs can be used as a marker for improvement in PES hypertonicity.² The relaxed PES muscle complex also allows more fluent vibrations of the underlying mucosa, thereby allowing for longer phonatory times. Hamaker and Blom reported that 79% of their patients achieved optimal or near-optimal voice after injection, as defined by 15–20 uninterrupted syllables and intra-tracheal pressures of 20–40mmH₂O upon manometry.¹⁶ Our results are comparable, with 7 of 8 patients showing a reduction in APMs after injection and 75% of intra-tracheal pressures within the range of 20–40cmH₂O post-injection. In addition, the anticipated increase in maximum phonatory times for a sustained vowel was seen in our study, with increases of 63% after injection.

In recent years, the importance of health-related QoL has been realised, and it is now widely considered an important outcome parameter for oncology of the head and neck.¹⁷ Moreover, patient-reported outcomes are important

for surgeons to provide evidence of benefit of their interventions and enhance their ability to counsel patients regarding therapeutic decisions and expected outcomes. Multiple questionnaires have been developed in this regard, and may be used longitudinally to evaluate changes over time and after interventions.

Our study is the first to introduce QoL as an outcome parameter for use of botulinum for treatment of PES. We utilised three questionnaires: UW-QoL, MDADI and VHI-30. These questionnaires were chosen to independently assess different issues influencing patient-perceived benefit. Each questionnaire has been validated for use in the context of surgery of the head and neck,¹⁰⁻¹² and is completed by the patient to avoid clinician bias.

Perhaps surprisingly, evaluation of the completed questionnaires highlighted disparities in score improvements after injection between different outcome measures. MDADI questionnaires showed a convincing improvement (10.3%) after injection. However, the improvements seen in UW-QoL questionnaires were less convincing (7.6%) and those in VHI-30 questionnaires even less so, with deterioration for the entire group of 2% but an improvement of 8.7% when considering patients whose indication for injection was difficulties with voicing. These findings suggest that patients who are aware of difficulties with voice gain benefit from the procedure, but those who did not consider themselves to be affected at presentation may have felt that botulinum impacted undesirably upon certain voice characteristics. Indeed, data collated as part of our measurements of digital

voice recording with respect to sustained vowel amplitude and frequency support this notion. Reductions in amplitude and frequency observed after botulinum injection were anticipated, and further support effective treatment of PES hypertonicity. However, it is plausible that such effects on voice are recognised by patients as a weakening and deepening of their voice, and so may be disliked.

It has been suggested that high pressure within the PES can lead to pooling of fluids around the posterior flange of trans-oesophageal prostheses, thereby causing forced opening of the valve and CVL.⁵ We observed a reduction in the number of valve changes required by patients after injection, supporting the notion that decreasing pressures within the PES reduce CVL. Data for comparison are extremely limited, but these findings are in accordance with earlier observations.^{1,5} To crudely assess the cost efficacy of treatment, we considered costs in the context of valve changes. The cost of a speech valve to our department is £120. Therefore, the overall net reduction of 12 valves in the year after injection resulted in a cost saving of £1,440. With regard to the cost of botulinum injections, one Dysport® 500-unit vial costs £142. If possible, a single vial was split between 2 patients, which resulted in the use of 10 vials in total, at a cost of £1,420. Therefore, the cost of Dysport® was recouped by the cost savings brought

Figure 4 Number of valve changes required in the year before and after botulinum injection for individual patients

about by reduced requirements for speech valves. We did not allow for other associated costs (eg VF use) but these costs could be counterbalanced by the reduced frequency of attendance at outpatient consultations, and reduced requirements for valve changes. In addition, use of botulinum for PES spasm is more cost-effective than alternative interventions (eg secondary surgical myotomy).

In addition to being efficacious, botulinum injection into the PES carries low risks for side-effects and complications in comparison with treatments advocated previously. Scott *et al*⁷ reported a prevalence of complications from secondary myotomy of $\leq 17\%$. In our study, all injections were carried out as outpatient procedures, and were well tolerated with no complications. These findings are in accordance with other studies in which few complications have been reported. One study reported 1 case of dysphagia after injection, whereas another study stated that 1 patient experienced regurgitation when lying supine.^{6,16}

Conclusions

The present study is the first to appraise the value of botulinum for PES spasm objectively and subjectively, and one of very few to evaluate its effect upon CVL. Within the limitations of this small-scale study we demonstrated the objective efficacy and safety of the procedure in treating dysphonia, dysphagia and CVL due to PES spasm. Our preliminary data also suggest it to be a cost-effective option, which is highly relevant in the environment of fiscal austerity within the UK National Health Service. To lessen the

risk of spasm and spasm-related disorders, treatments must reduce the tone of the neopharynx to be effective. Therefore, as shown in the present study, appropriate and effective injection of botulinum must reduce the frequency of the vibrating PES. We demonstrated how this effect is perceived by the patient, and highlights the resulting changes to voice that may occur as a result of the procedure (even if such changes are not the goal of the injection) may be recognised and considered undesirable. This phenomenon merits evaluation in future studies with a larger study cohort and, if confirmed, may have implications for counselling patients with regard to the outcome of the procedure.

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