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Vocal Exercise Versus Voice Rest Following Botulinum Toxin Injections: A Randomized Crossover Trial

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Abstract

Objectives—The intensity of muscle activity immediately following intramuscular botulinum toxin injection may affect the clinical efficacy of the injection. We tested this effect in patients who underwent botulinum toxin injections for adductor spasmodic dysphonia.

Methods—Patients were studied over 3 to 5 injection cycles. Cycle 1 was the baseline control; cycle 2 was randomized between a 1-hour reading aloud task (“exercise”) and a 24-hour period of complete voice rest. For cycle 3, the patient completed the task not performed in cycle 2. Patients who were willing to continue for cycles 4 and 5 repeated the experiment at one half the injection dosage. Efficacy was determined with a battery of voice recordings and clinical outcomes instruments administered via telephone at 2- to 4-week intervals. The primary outcome measure was the result of the Voice-Related Quality of Life (VRQOL) instrument.

Results—Nine patients (8 women, 1 man) with a mean age of 60.8 years (range, 42 to 76 years) completed at least 3 injection cycles. The VRQOL results were significantly higher for cycles that followed the exercise task. The patients reported subjectively that these were some of the best injection cycles they had ever experienced. Some achieved equivalent results with the half-dose injection plus exercise. The VRQOL results after voice rest cycles were not significantly different from the patients' baseline cycles.

Conclusions—These results support the conclusion that a period of intense vocalization immediately following laryngeal botulinum toxin injections improves the efficacy of the injection. Possible mechanisms are proposed.

Keywords

botulinum toxin; injection; quality of life; spasmodic dysphonia

Introduction

Laryngeal muscle injections with botulinum toxin are currently the most common form of treatment for patients with adductor spasmodic dysphonia.¹⁻⁸ Although the general efficacy of this treatment approach is well established, the treatment is not ideal, as there is an initial postinjection period of breathy dysphonia that lasts for 1 to 4 weeks, and there is another period of suboptimal voice during the last several weeks as the injection wears off. The

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portion of each injection “cycle” in which the patient's voice is significantly improved over his or her untreated baseline, based on quality-of-life measures, may be less than 50%.⁹

The clinical response to botulinum toxin injections in patients with adductor spasmodic dysphonia may vary from one injection cycle to another, despite use of the same dose, target muscle(s), and monitoring method. Possible explanations for this finding include variabilities in the exact location of the injection needle within the target muscle, in the precision of measuring and delivering small volumes of injectate, in the fraction of neuromuscular junctions that remain blocked from the previous injection, in technical aspects of reconstituting the freeze-dried toxin, and in the degree to which the new injection volume diffuses to nearby muscles and within the injected muscle.

Several animal and human studies report that injected toxin diffuses beyond the site of injection. Borodic et al¹⁰ demonstrated a within-muscle, dose-dependent diffusion gradient of botulinum A toxin injections in a rabbit model. Lee and Paniello¹¹ found that another neuromuscular blocker, vecuronium, diffuses beyond the injected muscle to affect nearby laryngeal muscles in a canine model. Diffusion effects have also been documented in clinical studies. Wohlfarth et al¹² used electromyography to document “modest” diffusion of botulinum A toxin into nearby forearm muscles in healthy volunteers. Hsu et al¹³ found a 50% wider area of affected forehead muscles by injecting the same botulinum A toxin dose in a five-fold higher volume. Comella et al¹⁴ radiographically documented an increase of up to 50% in peristaltic wave changes during swallowing following cervical injections of botulinum A toxin for torticollis.

Theoretically, a patient's voluntary muscle activity immediately following the injection could affect toxin diffusion. Repeated contraction-relaxation cycles could increase distribution within the muscle, potentially blocking more neuromuscular junctions. Muscle contraction has been shown to increase the effect of the botulinum A toxin in rat phrenic nerve–diaphragm preparations¹⁵ and in spastic human muscles that contract with electrical stimulation.¹⁶⁻¹⁸ Alternately, it could be hypothesized that this same “pumping” action could extrude some of the injected toxin from the muscle into the paraglottic space, in which case it would be ineffective.

Chen et al¹⁹ performed a randomized crossover trial in patients with writer's cramp dystonia. Immediately after botulinum A toxin injection into the forearm, the patients were either immobilized for 30 minutes, or wrote continuously for 30 minutes; at the next injection date, they did the opposite task. Strength measurements were made at 3 intervals during the injection cycle. The investigators found that the writing task led to a strength reduction that was 10% to 20% greater than that following the immobility task, but that the duration of effect was not affected. Their data support the hypothesis that postinjection muscle contraction affects the distribution of the toxin within the muscle. It also suggested that the planned use of some type of postinjection exercise might allow the use of lower doses of the toxin to achieve a similar clinical effect.

We hypothesized that intense vocal exercise after botulinum toxin injections may enhance the clinical effects in patients with adductor spasmodic dysphonia.

Materials and Methods

This study was approved and monitored by the Institutional Review Board of Washington University. Patients with a diagnosis of adductor spasmodic dysphonia and a demonstrated history of successful responses to botulinum toxin injections were invited to participate. To be eligible, patients were required to have 3 successive injection cycles with an established toxin dose and a consistent response.

The 5-cycle algorithm was carried out as shown in Fig 1. For cycle A (baseline), no special instructions were given after the injection. When the patient returned for cycle B, he or she was randomized to either the “rest” or “exercise” task, performed immediately after the injection. For the rest task, the patient was asked to remain on complete voice rest for 24 hours. For the exercise task, the patient was asked to read aloud for 1 hour some material of his or her choice, at a volume that could be heard through a closed door. If the volume fell below an audible threshold, the patient was prompted to increase his or her loudness effort. For cycle C, the patient performed the task not performed in cycle B. In the first 3 cycles, the patient received the previously established dose. For cycle D, the dose was reduced by one half and the exercise task was performed. The patient was blinded to the actual dose given. For cycle E, the half dose was injected and the rest task was assigned. At the time of each injection, the patients were asked to provide any subjective impressions about the effectiveness or quality of their voices during the previous cycle, and these were recorded in their charts.

The primary research question was addressed by study cycles A, B, and C. Given the expected length of the study (over 3 years for some patients), we were concerned about dropout, so the half-dose cycles were not randomized to early injection cycles, but were limited to cycles D and E. Similarly, we were more interested in half-dose exercise results than in half-dose rest results. Hence, cycle D was not randomized between exercise and rest, because of concern that after an ineffective cycle D injection, a patient might not be willing to continue for cycle E. However, significant dropout did not occur during the study.

Data collection for each cycle was performed on the day of injection, 2 days after injection, 5 to 7 days after injection, 2 weeks after injection, and then every 4 weeks through the end of the injection cycle, which was defined as the point at which the patient returned for the next injection. On the day of injection, data were collected “live” (not by telephone) before the injection. Subsequent data were collected by telephone at a day and time convenient for the patient, with a telephone cassette recorder (Radio Shack model TCR-200). The patients kept a binder containing copies of the reading passage and survey questions near the telephone to facilitate data collection. We previously demonstrated the efficacy of these telephone assessments.⁹

Each data set included the Voice-Related Quality of Life (VRQOL) instrument, with some supplemental questions; the Perceived Stress Scale instrument; a standardized reading passage (“Rainbow”); and sustained /i/ for maximum phonation time measurements.

The 10-item VRQOL instrument was chosen for obtaining voice outcomes data because of its brevity and demonstrated validity in this patient population,^{6,7} and it was the primary outcome measure for this study.

The VRQOL scores were calculated at each data collection interval, including the Physical Functioning and the Social-Emotional subscores, as defined by the validated survey instrument.²⁰ Data analysis was performed as described previously, with interpolation used to generate values at each decile, which were then averaged across all study participants.⁹ Results were compared with paired *t*-tests, and differences were considered significant for *p* values of less than 0.05.

Results

Nine patients (8 women, 1 man), with a mean age of 60.8 years (range, 42 to 76 years), entered the study and completed at least the first 3 cycles. The mean cycle length was 29.7 weeks (range, 12 to 56 weeks), and the mean number of data sets per patient per cycle was

8.0. A total of 281 sets of data were collected. At cycle B, 6 patients were randomized to “rest,” and 3 to “exercise.”

The total VRQOL scores are plotted in Fig 2. Note that all of the data for the “rest” cycles (whether the patient was randomized to rest in cycle B or C) are averaged together; the same was done for the exercise cycles. It can be seen that in general, the VRQOL scores rose for the first 30% of each cycle, stayed at a plateau for several weeks, and then declined during the last 25% of the cycle; these findings are similar to those reported previously.⁹ The VRQOL scores for the rest cycle did not differ significantly from the baseline ($p = 0.6$). The scores for the exercise cycles were significantly higher than those of both the rest cycles ($p < 0.0001$) and the baseline cycles ($p = 0.033$). The differences were manifested primarily during the mid-portion and later portions of the cycle; no difference was seen during the first 20%.

The VRQOL subscales also differed significantly, with the Social-Emotional subscores significantly higher than the Physical Functioning subscores ($p < 0.0001$). An example for the composite results following the full-dose exercise cycles is shown in Fig 3. These results are also consistent with our previous findings.⁹ The 10-item VRQOL includes 4 questions that constitute the Social-Emotional subscore, and 6 that are classified as indicating Physical Functioning. Thus, the “total” score is an average that is weighted 60% by the Physical Functioning subscores.²⁰

After the exercise cycle, the patients' free-form comments indicated that these were some of the best injection results they had ever had. The word “best” was used specifically by 4 of the patients, after an exercise cycle. Similar comments were not elicited from any patient after the rest cycles.

Eight of the 9 patients (7 women) allowed the half-dose injections for cycles D and E to be given, but complete data sets were obtained from only 4 of these patients. One of the patients requested a reversal of sequence of cycles D and E, which was accommodated. A typical set of total VRQOL results for all 5 cycles in a single patient is shown in Fig 4. It can be seen that cycle B (exercise in this case) gave VRQOL results better than baseline (cycle A), whereas cycle C (rest) was about even with the baseline. Cycle D, with exercise but with only half the usual dose, still gave a result about even with baseline, and cycle E, with rest and the half dose, was not as good as baseline. Subjectively, 1 of the patients used the word “best” to describe the results following a half-dose exercise cycle. Interestingly, among the half-dose groups, the exercise group had significantly higher VRQOL scores than did the rest group during the first halves of the injection cycles; in the second half, the scores evened out (ie, the reverse pattern of the full-dose groups).

At the completion of the study, for the patients' next injections, they were unblinded and informed that cycles D and E had been given at the half-dose level. They were then asked what dose they wanted to use for the next injection (given that day). Six of the 8 patients chose to continue with a dose reduction, 3 at the same half dose they had received in cycles D and E, and 3 at an intermediate level of about three quarters of the original dose (ie, 6 patients chose to continue with a 25% to 50% dose reduction).

Discussion

This study supports the idea that active muscle contraction following a botulinum toxin injection helps to distribute the toxin to more neuromuscular junctions, producing a more effective block. Although it was not possible to directly measure the strength of contraction of the injected laryngeal muscles, as done by Chen et al¹⁹ with the forearm muscles, the quality-of-life measures served as indirect indicators. The VRQOL instrument is a global

measure that includes Social-Emotional factors as well as Physical Functioning, perhaps providing an additional proxy for how well the strength reduction translates into reduced spasmodic activity of the laryngeal muscles, and how much dysphonia affects the patients' overall well-being. These results would seem to indicate that neuromuscular blockade achieved after the exercise task was more complete than that achieved in the other groups. The duration of action was not significantly affected, however, as is also consistent with the results of Chen et al.¹⁹

Previously, our practice was to allow patients to use their voices any way they wish after a laryngeal botulinum toxin injection. Presumably, the amount of talking, and perhaps the loudness, are related to the frequency and intensity of laryngeal muscle contractions; but without specific postinjection instructions, the amount of "vocal exercise" that occurs is likely to vary randomly for each patient and across patients. This may account for some of the cycle-to-cycle variability that patients experience; perhaps a deeper, more complete block of the laryngeal adductor muscles would reduce such variation. The exercise task for this study was intentionally extreme; it is not known whether a lesser amount of vocal activity might achieve the same result. We speculate that a reasonable postinjection instruction for the patients might be to ask them to read aloud for 15 minutes, and then also to encourage them to use their voices more than usual for the next few days.

Chen et al¹⁹ suggested that the greater effect achieved with exercise immediately after a botulinum injection could permit equivalent clinical benefit from lower doses of toxin. For large muscles, this could save tens or even hundreds of units, and a dose reduction can reduce the cost of the toxin and potentially reduce the risk of development of an immune response. For the small laryngeal muscles with small doses, this effect is probably not significant. More significant is the ability to maintain consistent responses to each injection. It was interesting that most of the patients opted to continue with a 25% to 50% dose reduction (from their original, established dose) for injections following the study. This choice may reflect recall bias of the more recent excellent results from the cycle of a half dose with exercise.

Although this is a small study, the randomized, single-blinded crossover design and the frequency of data collection strengthen the validity of the conclusions. An additional study, using a more modest exercise regimen that is clinically practical, would be a logical next step.

Conclusions

A period of intense vocal exercise immediately following laryngeal botulinum toxin injections appears to improve clinical benefit, as measured by VRQOL measures. If used routinely in postinjection instructions to the patient, this simple adjunct measure could reduce the variability in response that is normally experienced and improve patient satisfaction with this treatment approach.

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Fig 1.
Study protocol.

Fig 2.
Composite total voice-related quality of life (VRQOL) scores for 9 patients from study cycles A, B, and C.

Fig 3. VRQOL subscale scores for composite exercise cycles. Top scale is Social-Emotional subscale; lower curve is Physical Functioning subscale. Total score, shown with dotted line, is weighted average of two subscales.

Fig 4. Typical total VRQOL scores for 5 study cycles in single patient. Arrows indicate dates of botulinum toxin injections. Relative benefit plateaus are representative of overall study results (see text).