Reviewer's report

Title: Unilateral versus bilateral thyroarytenoid Botulinum toxin injections of in adductor spasmodic dysphonia

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Reviewer: James P Thomas

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1 Overall, this was an informative article. Primarily, it was very helpful to learn how others are performing laryngeal botulinum toxin injections, with what drug, with what technique and with what dose. Using the given set of data in the paper, I would not reach the same conclusion as the authors that unilateral injections are superior to bilateral injections.

Positives:

2 I would concur with the conclusion that there was no difference between unilateral and bilateral duration of response times in this study.

Concerns:

3 How were patients chosen to receive unilateral vs bilateral injections? What is meant specifically by "Dose and unilateral/ bilateral injections were determined by clinical judgment based on previous response?" If most patients were offered unilateral injections first, then I would be very concerned about selection bias (as the authors did allude to), but why not tell us the rationale behind the authors choices. How did the authors propose to the patient that they choose bilateral or unilateral injections. Did the recommendations of the author to the patient change over the course of the study, since this was not a randomized, prospective study?

4 On page 8, does clinical judgement mean the examiner injected unilaterally when one side appeared to spasm more on endoscopy? or was the injection side chosen randomly?

5 Total voice loss: In my experience, once a patient has reached a stable dose (which was an entry requirement for this study), they have no total voice loss and I perform all bilateral injections, so my perception is that total voice loss is dose related and in this study, the dosing in bilateral patients was double the dose in unilateral patients (6.6 vs 3.6), which could easily account for the 9 episodes of total voice loss in the bilateral group with none in the unilateral group.

6 Timing: The authors state "The time interval between injections was determined by comparing dates of the previous and current Dysport® injections. " In my experience this is quite inaccurate at tracking duration of response. I try to account for the actual duration of effect of the drug when gathering data by asking when the injection's beneficial effect wore off and that interval (between
end-of-effect and actual appointment) can easily range from a few days to many months, because of personal rather than medical issues (see Chang et al below).

7 Comments on pages 10 and 11. If a difference is not statistically significant, then it is not a trend! The following comments about "trend" should be removed from the article:

"Our study revealed greater mean dysphagia duration and a shorter breathiness with the bilateral injections but the difference in duration of these complications between unilateral and bilateral treatments were not statistically significant."

and

"However, the unilateral group has a trend to lower complication rate as would be expected." (in fact, this statement demonstrates a strong bias on the part of the author by the statement "as would be expected")

and

"Even though there is a trend with unilateral injections having a longer duration of action this is not statistically significant."

The only reasonable conclusion is that "There was no significant statistical difference between unilateral and bilateral groups, which both had similar rates of complications"

8 Intuitive?

What is the evidence for scarring of the injection tract? and is there evidence for positive or negative clinical impact if there is scarring of the injection tract? and why intuit that repeat injections may later have adverse effects on voice, which intuitively would be worse as the numbers of injections increases. - perhaps repeat injections leads to some overall benefit. (As I listen to voice recordings when patients say "all the botox is gone" from a previous injection, their voice, after years of injections, at it's worst is still improved from pre-injection voice recordings. So, I would intuit the opposite of the authors, that over time there is some permanent benefit from repeated injections, but the answer remains unknown.

9 A note:

The authors report on page 5 that in their review of the literature, "Bilateral doses reported to vary between 2.0 mu [10] and 2.5 mu [6,9,11,13] for each side." A report of mine (Chang, CY, Chabot, P, Thomas, JP.: "Relationship of Botulinum Dosage to Duration of Side Effects & Normal Voice in Adductor Spasmodic Dysphonia." Otolaryngol Head Neck Surg. 2007 Jun;136(6):894-9) had a mean of 1.6 units per side (median 0.67 units per side) with a range of 0.25 to 7.5 mu per side - which is quite a different range from their referenced papers, in particular the mean and median doses were much lower and if the authors conversion ratio between Botox and Dysport is correct, very similar to the doses used in this study.
10 Organization.

page 16. the paragraph at the top seems related to the paragraph at the bottom. On initial reading, I did not understand the paragraph at the top, specifically, "Our results may support the cumulative dose theory propagated by others [18,23,24]."

11 spelling on page 19. shouldn't "necessary" be "necessarily"?

12 Conclusion:

While the authors hone in on a dose of Dysport to be utilized, without knowing their selection bias, I could not agree that they can determine whether treatment should be unilateral or bilateral.

I would conclude from the article that unilateral low dose botulinum toxin injections are worth a try, but wouldn't quite reach the conclusion that they are the preferred treatment based on this study.

13 Page 13. I would concur strongly that accurate placement allows lower dosing and that would go along with my personal findings (2007). I couldn't tell from this study that the neurophysiologic scoring system (NPS) is any more helpful than injecting botulinum toxin at the point of maximum loudness when using an EMG system connected to a speaker.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests. JPT