Spasmodic Dysphonia Pain Study

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MAYO CLINIC

General Study Information

Principal Investigator: Dr. William Karle

Study Title: Spasmodic Dysphonia Pain Study

Protocol version number and date: Version 1. 07/05/20

Research Question and Aims

Hypothesis: The use of local anesthetic or vibrating instrument will decrease overall pain experienced by a patient with spasmodic dysphonia undergoing Botox injections.

Aims, purpose, or objectives: To identify adjuvant methods to improve patient comfort during in-office laryngology procedures. Results demonstrated here should be transferrable to other transcutaneous in office procedures in laryngology.

Background (*Include relevant experience, gaps in current knowledge, preliminary data, etc*.):

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BACKGROUND AND SIGNIFICANCE

Spasmodic Dysphonia (SD)

Spasmodic dysphonia (SD) is a task-specific focal laryngeal dystonia characterized by irregular and uncontrolled voice breaks that interrupt normal speech flow.[1] The condition was first described by Critchley in 1939 and was for some time considered a psychiatric disorder.[2] The estimated prevalence in western society is between 1 in 50,000 and 1 in 100,000.[3,4] There are likely multiple neurological processes involved in the pathophysiology of SD: reduced cortical inhibition, sensory-processing and reflex disturbances, and neuroanatomical findings at several different levels. Thus, SD should be considered an integrative system disorder, rather than a disorder with a single pathological focus.[1] Its etiology is multifactorial, including neurological, genetic, and environmental factors. Epidemiological risk factors have been suggested from several large cohort studies. The most commonly identified characteristics are females in their middle decades of life, a family history of neurological diseases including dystonia, recent life stressors, upper respiratory tract infections, and a history of childhood measles or mumps.[1] The eventual development of SD may be viewed as a multiple-hit mechanism, with endogenous predispositions and environmental triggers resulting in the development of its phenotype. Adductor spasmodic dysphonia (AdSD), characterized by a harsh, strain-strangled voice with breaks on vowels in speech, is the most common variant of the condition.[5] Vocal tremor co-occurs in 30% to 60% of AdSD patients.[1,5]

A three-tiered approach, involving clinical history, followed by speech assessment and in-office laryngoscopy is the most widely accepted method for making the diagnosis of SD.[5] Diagnosis is often made years after symptom onset and following assessment by numerous physicians.[6] In clinical practice, a history of speech therapy failing to ameliorate symptoms and positive treatment response to botulinum neurotoxin is a reliable adjunct to diagnosis. Botox (onabotulinumtoxinA) is the most frequently used and studied formulation of botulinum neurotoxin.

Based on the significant symptom response of blepharospasm to intermittent injections of Botox, Blitzer et al. performed the first laryngeal injection of Botox for SD in 1984.[7,8] Botulinum neurotoxin is internalized at the nerve terminal and works by cleaving proteins in the SNARE (soluble n-ethylmaleimide-sensitive factor [NSF] attachment protein receptor) complex, which facilitate the binding of vesicles containing acetylcholine to the nerve terminal.[9,10] Botulinum neurotoxin cleaves SNAP-25 inhibiting presynaptic acetylcholine release and muscle activity.[9] The precise mechanism by which botulinum neurotoxin improves SD symptomatology is unknown. Its effect is not fully explained by chemodenervation of the thyroarytenoid muscle since other adductor muscles are relatively unaffected and some patients experience improvement in concurrent extralaryngeal dystonias.[9] It may therefore result in disease modulation at a central level.[11]

Despite its use in the larynx being considered “off-label” by the U.S. Food and Drug Administration (FDA), botulinum neurotoxin has remained the first-line treatment for spasmodic dysphonia.[12] botulinum neurotoxin is the recommended primary management strategy in the American Academy of Otolaryngology-Head and Neck Surgery’s Clinical Practice Guideline for dysphonia.[13] Alternative treatment options for SD include surgical treatments, which include thyroarytenoid myotomy/myectomy, thyroplasty, selective laryngeal adductor denervation-reinnervation, laryngeal nerve crush, and recurrent laryngeal nerve resection.[14] There are no published randomized controlled trials comparing the effect of Botox injections and surgical treatment.[14] A systematic review published in 2017 reported that preference for one treatment could not be demonstrated.[14] The effect of bilateral Botox injections was evaluated and the authors found an improvement in the objective outcome, subjective outcome, and quality of life. The mean duration of effect ranged between 14 and 18 weeks. There is currently no cure for the condition. Thalamic deep brain stimulation may become a future treatment option to interfere with the central pathophysiology of SD.[15]

Laryngeal Injections

In-office procedures are increasingly common in laryngology.[16] Their success is dependent on adequate analgesia, and while these procedures are generally considered to be well-tolerated, few studies address pain or patient experience. A systematic review published in 2019 analyzed the literature for studies reporting qualitative or quantitative data for periprocedural pain assessment in adult patients undergoing in-office otolaryngology procedures.[16] A total of 86 studies met inclusion criterial, of which 31 related to laryngology. Of the 86 studies, only 13 were prospective studies comparing interventions and none of these studies addressed analgesia in laryngeal injections.[16] This study will be the first to compare the impact of anesthetic techniques in laryngeal injections.

Vocal fold injections (VFI) are commonly performed in-office procedures in laryngology that can be used as a treatment modality in vocal fold paralysis and in a number of other laryngeal pathologies, in addition to enabling the injection of botulinum neurotoxin in the treatment of SD. These can be performed transcutaneously (with multiple techniques), transnasally, or transorally. The transcricothyroid approach (a needle is passed through the skin, soft tissue, and cricothyroid membrane) is the most studied technique overall. Specific to the treatment of SD, a transcricothyroid approach is favored by 90% of laryngologists treating SD with botulinum neurotoxin.[12]

The patient experience and pain associated with laryngeal injections have been previously studied.[17,18,19] Young et al. reported the patient tolerance of 154 in-office laryngeal procedures including 108 VFIs, of which 8 were Botox injections.[17] Transcutaneous VFI was performed following injection of subcutaneous local anesthetic. The rate of completion of the first-choice VFI approach was 93%. Average patient-reported pain on the VAS was approximately 40. There was no statistically significant difference in pain between percutaneous and per-oral VFI approaches (VAS 43.1 versus 38.4). Discomfort score differed significantly between those patients who had a VFI successfully completed with the first-choice VFI technique versus those who required more than one VFI approach (36.03 versus 61.29).[17] Birkent et al. enrolled 26 patients receiving VFI with a transcricothyroid approach under local anesthesia with a mean reported VAS of 44.[18] Crawley et al. enrolled 45 patients to study the perception and duration of pain after VFI.[19] Injection was performed with a transcricothyroid approach following local and topical anesthesia. Almost 80% of patients reported increased pain from baseline to during the procedure and from baseline to after the procedure. The majority of patients reported that their pain persisted or worsened during the first post-procedure day. Almost half of patients took additional pain medication. A third of patients were still experiencing some discomfort on the third post-procedure day. They found that the magnitude of the increase in pain during the procedure was significantly associated with the presence of pain on the third post-procedure day. This data supports the hypothesis that nociceptive sensitization is responsible for lingering pain. In this study, patients reported a significant increase in sickening and punishing sensations as well as exhaustion and fear during the procedure.[19]

None of these studies controlled or compared anesthetic techniques. In each of the aforementioned studies, subcutaneous local anesthetic was delivered prior to transcutaneous injections. However, one-third of laryngologists report not using local anesthesia when treating SD with Botox.[12] Nor were alternative anesthetic techniques utilized.

Vibration Anesthesia

Vibratory stimulation is defined as the performance of continuous, quick, slight shaking movements on the skin using devices or fingers.[20] The application of a vibratory stimulus has been shown to improve patient discomfort associated with various needle-related procedures including botulinum neurotoxin injections for cosmetic indications.[21] The application of intense stimuli to the skin as a means of pain relief is not a novel concept.[22] Countless generations of bruised knees have been taken to mother so that she could "rub it to make it better". Ancient Greeks used vigorous massage to deal with sporting injuries, and by the early renaissance, de Mandeville was able to include percussion as a recognized treatment for pain. Percussion analgesia for amputation stump pain was recognized in the aftermath of the American Civil War, but this approach was not reported until the mid-1940s.[22]

In the 1960s a mechanism for the anesthetic capability of vibration was proposed. Melzack and Wall's "gate control" theory of pain postulates that the intensity of pain can be reduced by concurrent non-noxious stimulation, such as vibration.[23] Their hypothesis states that the transmission of the sense of vibration from mechanoreceptors located in the skin via A-β nerve fibers results in the shutting down of a "gate" through which pain signals are transmitted to the brain through A-δ and C fibers.[23] Despite this physiologic concept being well-recognized, in addition to much empirical evidence existing to support its validity, prospective controlled trials assessing its utility during awake procedures have only recently been produced.

A number of studies exist in the facial plastic surgery literature analyzing the analgesic properties of vibratory stimulation while performing cosmetic injections.[21,24-26] Sharma et al. applied a vibratory stimulus during the cosmetic facial injection of Botox.[21] There was a statistically significant reduction in patient's pain scores (1.3 vs 2.4 on a five-point Likert-type scale). Of the 50 patients, 82% noted that the vibration side of the face had lower pain than the side of their face injected without vibration. Further, 86% these patients preferred to utilize vibratory analgesia for subsequent injections.[21] Mally et al. applied a vibratory stimulus during injection of the nasolabial folds with dermal filler.[24] They found improved patient tolerance with vibratory stimulation. While 88% of patients found the injections moderate to severely painful without vibration, only 14% with vibration experienced moderate to severe pain.[24] This finding was replicated by Guney et al. in a randomized split-lip study assessing vibration anesthesia during lip augmentation with cosmetic filler.[25] The overall pain score on the vibration-assisted side was significantly reduced (3.8 vs 5.6 on a ten-point Likert-type scale). Of the 25 patients enrolled in this study, 23 stated that they would want to have vibration anesthesia for future injections. The 2 patients who declined vibration stimuli for the future stated that they felt an increase of pain and anxiety with the addition of vibration. Both of these patients underwent lip augmentation for the first time. All patients that had undergone previous lip augmentation treatments expressed a desire for vibration anesthesia in the future.[25] Chorney et al. published a prospective, randomized, self-control trial of cosmetic botulinum toxin injections comparing vibration anesthesia to topical ice analgesia to no additional analgesia.[26] There were 30 injections given with vibration analgesia, with a mean VAS of 26.5. There were 28 injections given with ice that resulted in a mean VAS of 24.4. Among the 30 injections given without any analgesia, patients had mean VAS of 29.4. There was no statistically significant difference between these groups. Of note this study design resulted in a lack of power given only a maximum of 30 injections were present in each arm.

There is additional support for the analgesic properties of vibratory stimulation outside of the facial plastic surgery literature. A systematic review evaluated evidence of the effectiveness of vibratory stimulation to reduce needle-related procedural pain in children.[20] The meta-analysis of this systematic review showed

that vibratory stimulation was significantly effective according to both self-rated and observer-rated pain measurements regardless of age group, type of procedure, or type of vibration device.[20] Within the dermatology literature further support can be found. Park et al. studied VAS scores when vibration anesthesia was used during keloid triamcinolone injections. Intralesional injection therapy without vibration yielded mean VAS scores of 59 compared to 33 when vibration was used ($P < .05$).[27] Fix et al. studied vibration anesthesia during the injection of lidocaine in an open label, randomized, controlled, split-body trial. The median VAS pain score was 26 for injections without vibration versus 7.5 with vibration ($P<0.01$).[28]

However, no study to date has analyzed the use of vibration analgesia during VFI.

Study Design and Methods

Methods: *Describe in lay terms, completely detailing the research activities that will be conducted by Mayo Clinic staff under this protocol.*

Each patient will undergo each of the three treatment modalities. The order in which they receive these will be randomized.
Treatment Group A (control): No anesthesia
Treatment Group B: 0.5cc subcutaneous 2% lidocaine in 1:100,000 epinephrine (done approximately 2 minutes before Botox injection)
Treatment Group C: Vibrating instrument held adjacent to cricothyroid space as Botox injection is performed

The nurse assisting the procedure will also time the Botox portion of the procedure to enable analysis of whether pain is associated with longer procedure time.

Patient participation is expected to last approximately 6-12 months. The study specific questionnaire #1 will be given at only their first visit. Study specific questionnaire #2 will be given immediately after each Botox injection.

Subject Information

Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.

Target accrual: 50

Subject population (children, adults, groups): Adults with spasmodic dysphonia

Inclusion Criteria:

-spasmodic dysphonia with or without tremor
-receiving botox as treatment via a transcricothyroid approach

Exclusion Criteria:

-allergy to lidocaine

Biospecimens

Collection of blood samples. When multiple groups are involved copy and paste the appropriate section below for example repeat section b when drawing blood from children and adults with cancer.

a. **From healthy, non-pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.
   Volume per blood draw: _____ml
   Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

b. **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.
   Volume per blood draw: _____ml
   Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

Prospective collection of biological specimens other than blood: _____

Review of medical records, images, specimens

Check all that apply (data includes medical records, images, specimens).

☐ Only data that exists before the IRB submission date will be collected.

Date Range for Specimens and/or Review of Medical Records:
Examples: *01/01/1999 through 12/31/2015*, or all records through *mm/dd/yyyy*.

Note: The Date Range must include the period for collection of baseline data, as well as follow-up data, if applicable.

X☐ The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.
Examples

- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☐ The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.

Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____

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Data Analysis

Power analyses may not be appropriate if this is a feasibility or pilot study, but end-point analysis plans are always appropriate even if only exploratory. Provide all information requested below, or provide justification if not including all of the information.

Power Statement:
Sample size estimation is estimated based on the repeated methodology; that is, the VAS score will be measured at three time points (initial visit, 3 months and 6 months) for each patient. The comparisons between treatment arms (treatment B and C) and control arm (A) are of interest. To preserve the family wise type I error rate, 0.05, Bonferroni approach is used to adjust the pairwise type I error (0.05/2 = 0.025). We further assume the standard deviation across subjects at the same time point is 3.00, and there is a weak correlation between the VAS (<= 0.3) within each patient. To achieve 80% to detect statistically significant differences in the mean VAS between A and B, and between A and C, the required sample size based on different value of correlation are listed below:

VAS			Required sample size		
A	B	C	Correlation = 0.3	Correlation = 0.1	Correlation = 0.05
4	1	1	18	21	22

	2	2	32	40	42
	3	3	114	145	153
5	2	2	18	31	22
	3	3	33	40	42
	4	4	114	145	153
6	2	2	13	14	14
	3	3	18	21	22
	4	4	32	40	42
	5	5	114	145	153

Note: The weaker the correlation and the smaller the mean difference in VAS the larger the sample size. Randomization schedule will be generated by the study statistician. Randomization will determine the order they get these treatments and can follow any permutation.

Data Analysis Plan:

Data Handling

The study data will be entered and saved in REDCap. The REDCap database will be created by the study personnel. Only the PI and study personnel will have access to the database.

Data analysis

Data will be summarized by mean (standard deviation) or median (interquartile range) for continuous variables, and frequency count (percentage) for categorical variable. The number of patients without the VAS score at 3- and 6-months after the initial visit will be reported. Generalized estimating equation will be used to compare the mean VAS score between groups, and the point estimate of the mean difference and 95% confidence interval will be reported.

Endpoints

Primary: Response to the Visual Analogue Scale

Secondary: Patient preference regarding injection analgesia

REFERENCES

1. Hintze JM, Ludlow CL, Bansberg SF, Adler CH, Lott DG. Spasmodic dysphonia: a review. part 1: pathogenic factors. Otolaryngology–Head and Neck Surgery. 2017 Oct;157(4):551-7
2. Critchley M. Spastic dysphonia ("inspiratory speech"). Brain. 1939 Mar 1;62(1):96-103.
3. White LJ, Hapner ER, Klein AM, Delgaudio JM, Hanfelt JJ, Jinnah HA, Johns III MM. Coprevalence of anxiety and depression with spasmodic dysphonia: a case-control study. Journal of Voice. 2012 Sep 1;26(5):667-e1.
4. Konkiewitz EC, Trender-Gerhard I, Kamm C, Warner T, Ben-Shlomo Y, Gasser T, Conrad B, Ceballos-Baumann AO. Service-based survey of dystonia in Munich. Neuroepidemiology. 2002;21(4):202-6.
5. Patel AB, Bansberg SF, Adler CH, Lott DG, Crujido L. The Mayo Clinic Arizona spasmodic dysphonia experience: a demographic analysis of 718 patients. Annals of Otology, Rhinology & Laryngology. 2015 Nov;124(11):859-63.
6. Creighton FX, Hapner E, Klein A, Rosen A, Jinnah HA, Johns MM. Diagnostic delays in spasmodic dysphonia: a call for clinician education. Journal of Voice. 2015 Sep 1;29(5):592-4.
7. Blitzer A, Brin MF, Fahn S, Lovelace RE. Localized injections of botulinum toxin for the treatment of focal laryngeal dystonia (spastic dysphonia). The Laryngoscope. 1988 Feb;98(2):193-7.
8. Blitzer A. Spasmodic dysphonia and botulinum toxin: experience from the largest treatment series. European Journal of Neurology. 2010 Jul;17:28-30.
9. Novakovic D, Waters HH, D'Elia JB, Blitzer A. Botulinum toxin treatment of adductor spasmodic dysphonia: longitudinal functional outcomes. The Laryngoscope. 2011 Mar;121(3):606-12.
10. Humeau Y, Doussau F, Grant NJ, Poulain B. How botulinum and tetanus neurotoxins block neurotransmitter release. Biochimie. 2000 May 1;82(5):427-46.
11. Giladi N. The mechanism of action of botulinum toxin type A in focal dystonia is most probably through its dual effect on efferent (motor) and afferent pathways at the injected site. Journal of the neurological sciences. 1997 Nov 25;152(2):132-5.
12. Shoffel-Havakuk H, Rosow DE, Lava CX, Hapner ER, Johns III MM. Common practices in botulinum toxin injection for spasmodic dysphonia treatment: A national survey. The Laryngoscope. 2019 Jul;129(7):1650-6.
13. Stachler RJ, Francis DO, Schwartz SR, Damask CC, Digoy GP, Krouse HJ, McCoy SJ, Ouellette DR, Patel RR, Reavis CC, Smith LJ. Clinical practice guideline: hoarseness (dysphonia)(update). Otolaryngology–Head and Neck Surgery. 2018 Mar;158(1_suppl):S1-42.
14. Van Esch BF, Wegner I, Stegeman I, Grolman W. Effect of Botulinum Toxin and Surgery among Spasmodic Dysphonia Patients: A Systematic Review. Otolaryngology–Head and Neck Surgery. 2017 Feb;156(2):238-54.
15. Poologaindran A, Ivanishvili Z, Morrison MD, Rammage LA, Sandhu MK, Polyhronopoulos NE, Honey CR. The effect of unilateral thalamic deep brain stimulation on the vocal dysfunction in a patient with spasmodic dysphonia: interrogating cerebellar and pallidal neural circuits. Journal of neurosurgery. 2018 Feb 1;128(2):575-82.
16. Frank E, Carlson B, Hu A, Randall DR, Tamares S, Inman JC, Crawley BK. Assessment and treatment of pain during in-office otolaryngology procedures: a systematic review. Otolaryngology–Head and Neck Surgery. 2019 Aug;161(2):218-26.
17. Young VN, Smith LJ, Sulica L, Krishna P, Rosen CA. Patient tolerance of awake, in-office laryngeal procedures: a multi-institutional perspective. The Laryngoscope. 2012 Feb;122(2):315-21.
18. Birkent H, Sardesai M, Hu A, Merati AL. Prospective study of voice outcomes and patient tolerance of in-office percutaneous injection laryngoplasty. The Laryngoscope. 2013 Jul;123(7):1759-62.
19. Crawley BK, Dehom S, Kutzner E, Murry T, Krishna P, Hata J. Perception and duration of pain after office-based vocal fold injection augmentation. The Laryngoscope. 2018 Apr;128(4):929-34.
20. Ueki S, Yamagami Y, Makimoto K. Effectiveness of vibratory stimulation on needle-related procedural pain in children: a systematic review protocol. JBI Evidence Synthesis. 2018 Apr 1;16(4):825-30.
21. Sharma P, Czyz CN, Wulc AE. Investigating the efficacy of vibration anesthesia to reduce pain from cosmetic

botulinum toxin injections. Aesthetic surgery journal. 2011 Nov 1;31(8):966-71.
22. Vibration therapy for pain. Lancet. 1992;339(8808):1513-1514.
23. Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965 Nov 19;150(3699):971-9.
24. Mally P, Czyz CN, Chan NJ, Wulc AE. Vibration anesthesia for the reduction of pain with facial dermal filler injections. Aesthetic plastic surgery. 2014 Apr 1;38(2):413-8.
25. Guney K, Sezgin B, Yavuzer R. The efficacy of vibration anesthesia on reducing pain levels during lip augmentation: worth the buzz?. Aesthetic Surgery Journal. 2017 Oct 1;37(9):1044-8.
26. Chorney SR, Villwock JA, Suryadevara AC. Vibration Versus Ice to Reduce Cosmetic Botulinum Toxin Injection Pain—A Randomized Controlled Trial. Ear, Nose & Throat Journal. 2019 Jul;98(6):351-5.
27. Park KY, Lee Y, Hong JY, Chung WS, Kim MN, Kim BJ. Vibration anesthesia for pain reduction during intralesional steroid injection for keloid treatment. Dermatologic Surgery. 2017 May 1;43(5):724-7.
28. Fix WC, Chiesa-Fuxench ZC, Shin T, Etzkorn J, Howe N, Miller CJ, Sobanko JF. Use of a vibrating kinetic anesthesia device reduces the pain of lidocaine injections: a randomized split-body trial. Journal of the American Academy of Dermatology. 2019 Jan 1;80(1):58-9.