Treatment of Hypophonia with Collagen Vocal Fold Augmentation in Patients with Parkinsonism

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Abstract

Objective: To determine the impact on voice and quality of life by vocal fold collagen augmentation in patients with hypophonia associated with Parkinson's disease (PD) and other parkinsonian disorders.

Design: We conducted structured interviews of patients and their caregivers following vocal fold collagen injections. A voice quality questionnaire was developed to quantify the change in voice characteristics after treatment. The Glascow Benefit Inventory (GBI) was used to quantify the change in quality of life after treatment.

Results: A total of 12 patients (7 male, 5 female; average age 73.7 ± 8.6 years) completed the questionnaire having completed an average of 3.0 ± 1.7 collagen injections at the time of the interview with an average of 13.8 ± 7.4 weeks between each injection. The mean values for all six voice quality questions ranged from 3.6 – 4.2 on a scale of 1 (negative effect) to 5 (positive effect) with 3 being no change. Mean GBI total benefit score and GBI social subscore showed significant improvement ($p < 0.05$). On average, patients tolerated the injection procedure well and noted improvement immediately with an average duration of improvement of 7.8 ± 8.5 weeks. Two out of the 13 patients had an adverse event - one patient experienced temporary hoarseness and one had temporary difficulty swallowing following the injection. The average overall satisfaction score was 3.2 (equivocal) (on a scale of 1 – 5, 1 being completely dissatisfied and 5 being completely satisfied) and tended to correlate with GBI total score ($p = 0.08$) and duration of improvement ($p = 0.06$).

Conclusion: Despite the relatively small sample size, our study suggests that augmentation of vocal folds with collagen injections may provide improvement in voice quality in patients with parkinsonian hypophonia.

Background

One of the most disabling features of Parkinson's disease (PD) is speech and voice difficulty, affecting approximately 75-90% people with PD. [1] In his original 1817 Essay on the Shaking Palsy, James Parkinson attributed the voice disturbances in his patients with PD to some respiratory dysregulation by suggesting that they "fetched their breath rather hard". [2] Typically, the speech and voice quality in patients with PD tends to be low in volume, breathy, monotone, and slurred. In contrast to patients with essential tremor, PD patients rarely complain of shaky or tremor-like voice. These speech and voice abnormalities are even more troublesome in patients with atypical parkinsonism, such as multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). The inability to communicate effectively with family members, friends and coworkers can lead to feelings of isolation and frustration, resulting in a marked reduction in quality of life.

In contrast to the typical cardinal signs of PD (tremor, bradykinesia, and rigidity) that usually improve with levodopa, speech and voice problems continue to deteriorate despite dopaminergic therapy. [3] A variety of materials have been used to augment vocal folds in patients with PD and other disorders of the vocal cords in an attempt to increase voice volume. Polytetrafluoroethylene was used to augment vocal folds 20 years ago, but is less used today because of the risk of polytetrafluoroethylene to cause granulomas and its potential to migrate to adjacent structures. [4] Berke et al [5] reported improvement in quality of voice following transcutaneous bovine collagen augmentation of the vocal cords in 35 patients with idiopathic PD. The beneficial effects lasted an average of 12 weeks and there were no major complications. Seventy-five percent of the patients reported positive feelings towards the procedure (high marks for increasing voice loudness, decreasing social embarrassment, tolerance of the procedure and satisfaction; slightly less high marks for increasing voice clarity) and 16% reported dissatisfaction. We examined the effects of this procedure in 12 patients with PD, other parkinsonian disorders, and other vocal fold disturbances associated with severe hypophonia.

Methods

Seventeen patients with parkinsonism and severe hypophonia were treated at Baylor College of Medicine with vocal fold collagen augmentation between 1999 – 2002. We obtained follow-up information in 12 patients; three others were deceased at the time of follow-up, one refused to participate, and one could not be contacted. Of the 12, eight were diagnosed with idiopathic PD, two with vascular parkinsonism, one with MSA, and one with PSP. Despite varied diagnoses, all patients had similar subjective voice disturbances (low volume voice) and all demonstrated similar objective findings upon laryngoscopy: atrophy and bowing of the vocal folds with incomplete approximation resulting in a glottic gap.

While in the supine position, the patient's neck was extended and external landmarks identified to locate the cricothyroid membrane between the thyroid cartilage and cricoid cartilage. Topical 1% lidocaine with 1:100,000 epinephrine was injected at the site overlying the cricothyroid membrane. An Olympus flexible fiber optic laryngoscope, inserted through the nasal passageway, was used to visualize the larynx. A 27 guage needle was passed through the cricothyroid membrane and directed submucosally superiorly and laterally into the vocal cords. Approximately 0.5 – 1.5 cc of Zyderm 2 purified bovine dermal collagen was injected into each affected focal fold and paraglottic space. Improvement in the contour and shape of the vocal folds was directly visualized via the laryngoscope as the collagen was injected and closure of the glottal gap on adduction of the folds confirmed. Except for transitory hoarseness and dysphagia occurring in one patient each, no immediate or delayed complications occurred after the injection procedures.

Table 1. Patient Demographics (N = 12)

	Mean ± SD	Range
Age	73.7 ± 8.6	56.8 – 88.5
No. of years of parkinsonism	11.1 ± 5.7	4.0 – 22.0
Voice severity prior to injection	2.0 ± 0.9	1.0 – 4.0
Time interval between injections (weeks) [a]	13.8 ± 7.4	4.0 – 24.0
No. of collagen injections to date	3.0 ± 1.7	1.0 – 6.0
No. of years of voice disturbances	9.3 ± 5.8	3.0 – 20.0

[a] Not all participants had more than one injection at the time of interview (n = 8).

One patient received Zyplast, highly purified dermal bovine collagen lightly crosslinked with gluta-raldehyde, after receiving several previous injections with Zyderm that resulted in short-lived responses. Patients were instructed to return for a follow-up evaluation in one week.

Information regarding age at first collagen injection, sex, frequency of collagen injections, total num-ber of collagen injections at the time of the survey, years of voice symptoms, past voice treatment measures, and adverse events resulting from the collagen injections was obtained. A telephone survey was administered to the patients, caregivers, or both. Voice quality in response to collagen injections was assessed via a series of six questions focusing on the change in voice loudness, clarity, intelligibility, and quality and each item was rated on a scale of 1 (negative effect) to 5 (positive effect) with 3 being no change. [Table 2] The Glascow Benefit Inventory (GBI) is a validated questionnaire of 18 questions speci-fically developed to assess the change in health status following an otorhinolaryngological intervention. [6] A score between -100 to +100 was then calculated to assess change in quality of life. A positive score indicates a benefit in quality of life, a negative score indicates a negative impact in quality of life, and a score of zero indicates no change. The voice severity was rated on a 1 to 5 scale: 1 = aphonic, 2 = severe, 3 = moderate, 4 = mild, and 5 = normal voice. Replies for both questionnaires and questions concerning tolerability and overall satisfaction were based on the following 5-point scale: 5 - "much better", 4 - "better", 3 - "no change", 2 - "worse", 1 - "much worse". Additional information on day of improvement, day of maxi-mal improvement and duration of improvement was also investigated.

The data were analyzed using SPSS v10. A one-sample t-test using the mean value of no change (zero) was used to calculate p values for GBI scores. None of the above scores could be corrected for demographic differences due to the small patient population (i.e. univariate analysis of covariance with power << 0.8). Correlations were calculated using Spearman's rho. Demographic data, voice quality questions, tolerability, satisfaction and days of improvement were assessed via mean and standard deviation calculations.

Results

A total of 12 patients completed the questionnaire (7 male, 5 female; mean age 73.7 ± 8.6 years). The mean voice severity rating prior to injection was 2.0 (range 1 –4) or "severe" and defined as "difficulty initiating voice, poor intelligibility, reduced loudness, monotony, and breathiness". [7] Besides pharmacologic, dopaminergic therapy, previous treatments for voice dysfunction included bilateral subthalamic deep brain stimulation (DBS) and speech therapy (1 pt), DBS alone (1 pt), and speech therapy alone (4 pt). The mean number of collagen injections at the time of survey was 3.0 (range 1 – 6) and the average time interval between injections was 13.8 weeks. The mean number of years of parkin-sonian symptoms was 11.1 years and the mean number of years of voice difficulty was found to be 9.3 years. [Table 1]

The mean values for all six voice quality questions ranged from 3.7 to 4.2. [Table 2] Voice questions #3 ($r = 0.62$, $p < 0.05$) and #5 ($r = 0.64$, $p < 0.05$) correlated with the GBI total score. Question #5 also correlated with the GBI social subscore ($r = 0.65$, $p < 0.05$). Based on one sample t-tests, the mean GBI total benefit score and GBI social subscore showed significant improvement ($p < 0.05$). Neither the mean GBI general subscore nor the mean GBI physical health subscore were statistically significant. [Table 3]

On average, patients tolerated the injection procedure well with a mean tolerability score of 4.3 ± 1.1. All patients noted some effect immediately (i.e. on day zero) with an average duration of improvement lasting 7.8 ± 8.5 weeks. [Table 4] Two of the 13 patients reported an adverse event: hoarseness for several hours following the injection that resolved spontaneously (1 pt), and difficulty swallowing following the injection for approximately one day, resolving spontaneously (1 pt). The mean overall satisfaction score was 3.2 ± 1.2 (no strong feelings of either satisfaction or dissatisfaction) on a scale ranging from 1 (extreme dissatisfaction) to 5 (extreme satisfaction). Overall satisfaction tended to correlate with GBI total score ($r = 0.52$, $p = 0.08$), GBI general subscore ($r = 0.53$, $p = 0.08$) and duration of improvement ($r = 0.55$, $p = 0.06$). Additionally, duration of improvement correlated with GBI general score ($r = 0.76$, $p < 0.004$), but only tended to correlate with the GBI total score ($r = 0.53$, $p = 0.08$).

Table 2. Voice Quality Ratings After Collagen Injections (N = 12) [a]

	Mean ± SD	Range
When you were at your best after the collagen injection procedure...		
QV1: Did you feel other people had more or less difficulty hearing you as compared to before the procedure?	4.2 ± 0.7	3.0 – 5.0
QV2: Did you feel the volume of your voice was increased or decreased as compared to before the procedure?	4.1 ± 0.7	3.0 – 5.0
QV3: Did you speak with friends, neighbors or relatives more or less often as compared to before the procedure?	3.7 ± 0.8	3.0 – 5.0
QV4: Did you feel that people asked you to repeat yourself more or less often as compared to before the procedure?	3.9 ± 0.8	3.0 – 5.0
QV5: Did you feel the clarity of your voice was better or worse as compared to before the procedure?	4.1 ± 0.7	3.0 – 5.0
QV6: Did you feel the quality of your voice was better or worse as compared to before the procedure?	4.0 ± 0.4	3.0 – 5.0

[a] 1 (much worse) to 5 (much better, normal or nearly normal) with 3 being no change.

Discussion

This pilot, exploratory study provides evidence that collagen injections into vocal folds improves voice and quality of life in patients with hypophonia associated with parkinsonism. All 12 patients rated, on average, their voice quality responses better than "no change" (score of 3) indicating beneficial response after the collagen augmentation procedure. As a result of improved clarity, quality and volume of their voice, fewer people asked patients to repeat themselves and patients reported that it was easier to communicate with their friends and family. This was reflected in the statistically significant correlations between the voice quality, based on the voice questionnaire, and the validated GBI quality of life questionnaire.

There are many reasons why the response to collagen injections is not consistent between or within patients. Besides variable vocal fold approximation achieved with each collagen injection, partly dependent on the placement of the needle and volume of injected collagen, poor breathing effort, diminished physical and mental capacity, and phasic activity of the upper-airway muscles during respiration [8] may hamper the ability to produce sufficient voice volume. As the diaphragm is usually spared in PD, changes in airflow resistance, not driving pressure, cause airflow oscillations. While overall speech amplitude is reduced in patients with PD compared to normal controls during conversational speech, the voice regulation (rate of voice volume increase) is relatively well preserved. [9] PD patients are able to adjust voice volume but volume starts at a lower level that may be partly related to volume perception.

The collagen injections were well tolerated and the observed improvement in the GBI social score suggested that this treatment strategy improved the social aspects of quality of life, such as relationships with family and friends. The sample size, however, was too small to show statistically significant improvements in overall quality of life, general quality of life or physical health. Furthermore, the lack of statistical significance of scores may be also attributed to question #9 [6] which states: "Since your collagen injection procedure, do you feel more or less confident about job opportunities?" This question did not apply to this patient population since all patients were retired. Additionally, many patients commented that it was difficult to assess quality of life based strictly upon the collagen injections when other aspects of their health, especially their parkinsonian symptoms, were interfering with their overall quality of life. Patients were much less satisfied and had lower quality of life scores when positive effects of the augmentation were short-lived, even if the temporary gain in their voice volume was robust. Thus, duration of benefit is key to improving overall quality of life and voice function. This observation is in agreement with Berke et al [5] whose study showed that overall satisfaction with collagen injections correlated with duration of benefit ($r = 0.55$).

Table 3. The Glascow Benefit Inventory (GBI) Scores (N = 12)

	Mean ± SD	Range	p [a]	95% CI
Total Score	12.5 ± 18.8	-11.1 – 41.7	0.042	0.5 – 24.5
General Subscore	12.8 ± 25.1	-16.7 – 45.8	0.104	-3.1 – 28.8
Social Subscore	20.8 ± 24.7	0.0 – 66.7	0.014	5.1 – 36.6
Physical Health Subscore	2.8 ± 13.9	-33.3 – 16.7	0.504	-6.1 – 11.6

[a] One sample t-test (2-tailed)

Table 4. Tolerability, Satisfaction and Duration of Improvement After Collagen Injections (N = 12)

	Mean ± SD	Range
Tolerability	4.3 ± 1.1	2.0 – 5.0
Overall satisfaction	3.2 ± 1.2	1.0 – 5.0
Day of improvement noted [a]	0.0 ± 0.0	0.0 – 0.0
Duration of improvement (weeks)	7.8 ± 8.5	0.0 – 25.7

[a] 0 = Immediate improvement

The effects of the injection in our study lasted on average approximately 7.8 weeks (up to 25 weeks), within the range of duration demonstrated in the Berke et al [5] collagen study (average of 12 weeks, range from 4 – 52 weeks). Duration of benefit may be influenced by a number of factors, including the material properties of the collagen. Materials other than bovine collagen have been studied in the past including Teflon [4], autologous collagen and autologous fat. Autologous collagen is the bioimplant of choice for patients with hypersensitivity reactions to bovine collagen. However, a 30cm^2 area of skin is needed to create 2 ml of collagen, and this procedure leaves a permanent scar and it takes approximately 45 days for the collagen to be manufactured. A study of 8 patients with unilateral vocal fold immobility receiving autologous collagen vocal fold implants showed statistically significant improvement in quality of speech (i.e. maximum phonation time, mean flow rate, and buccal airflow), similar to bovine collagen studies. [10] Another option, autologous fat, is a readily available source; however, rapid resorption may occur. To investigate durability, 22 patients with either vocal fold atrophy or paralysis were followed for one year after autologous fat injection into the vocal folds. [11] A 4 cm^3 volume of fat was surgically excised from the patients and purified before injection. At the one, six, and twelve month follow-up visits, all patients showed statistically significant improvement in glottic closure as well as the patient's perception of grade of dysphonia severity, breathiness, effort and functional interference. No head-to-head comparisons of different materials for vocal fold injection over a long period of time have been studied.

Our study has several inherent limitations. This is a retrospective study without a place control or a comparison control group of patients not injected with collagen. Furthermore, the study sample was small and the patient population was quite heterogenous in terms of diagnosis and severity of impairment. Nevertheless, despite these limitations, our study suggests that augmentation of vocal folds with collagen injections improves voice volume, intelligibility and overall quality in patients with PD-related hypophonia. Furthermore, the procedure is well tolerated and appears to have a beneficial impact on the social aspects of quality of life. Controlled studies, however, are needed before this treatment strategy can be recommended routinely.

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