The Laryngoscope

Safety of Platelet-Rich Plasma Subepithelial Infusion for Vocal Fold Scar, Sulcus, and Atrophy

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Objective: To demonstrate the safety profile of platelet-rich plasma (PRP) as an injectable therapeutic for the treatment of vocal fold scarring and atrophy.

Methods: Preliminary report on a prospective clinical trial of patients with vocal fold scar or atrophy undergoing unilateral vocal fold subepithelial infusion with autologous PRP. Enrolled patients underwent four subepithelial injections spaced 1 month apart. Adverse events were assessed peri and post-injection at each session. Patient-reported outcomes were collected at every visit using the Voice Handicap Index-10 (VHI-10) and Vocal Fatigue Index (VFI) questionnaires.

Results: Twelve patients underwent unilateral vocal fold injection with autologous PRP prepared according to Eclipse PRP® system protocol. Forty-three injections were performed using a peroral or percutaneous approach. An average of 1.57 ± 0.4 cc (range 0.6–2.0 cc) injectate was used. All patients tolerated the procedure without difficulty or peri-procedural complications. The average duration of follow-up was 3.6 ± 1.8 months. No significant inflammatory reactions or adverse events were seen to date. There was statistically significant improvement in patient-reported outcomes at the 3 month follow up ($n = 9$) follow-up (mean ΔVHI-10 $= 10.8$, $p < 0.001$, mean ΔVFI $= 18.9$, $p = 0.01$, t test, paired two sample for means, two-tail). All nine patients who completed the series of four injections subjectively (yes/no) reported they were satisfied with the results.

Conclusion: This prospective study cohort demonstrated a favorable safety profile, with no adverse events or peri-procedural complications. Subjective improvements in vocal quality and reduction in vocal fatigue need to be clinically correlated with further study.

Key Words: platelet-rich plasma, vocal fold scar, superficial lamina propria, vocal fold atrophy.

Level of Evidence: 4

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INTRODUCTION

Vocal fold atrophy and scar are causes of dysphonia that pose major treatment challenges for laryngologists.[1] The etiology of vocal fold scar is diverse, potentially stemming from phonotrauma, phonomicrosurgery, iatrogenic injury, malignancy, and radiation therapy.[2,3] Additionally, loss of hyaluronic acid, elastic fibers, and lubrication during the aging process can reduce viable tissue mass.[4] Underlying alterations to the superficial lamina propria (SLP) of the vocal folds drastically alter compliance.[5] Consequently, patients endure considerable dysphonia, vocal fatigue, decreased volume, and altered pitch. These changes can contribute to depression, reduced social interaction, and decreased quality of life.[6]

The most common initial treatment for vocal fold atrophy condition is voice therapy administered by a specialized speech-language pathologist spaced out over multiple monthly sessions. Voice therapy introduces logistical strains in the elderly population, such as coordinating transportation across several sessions, and is limited by its inability to restore normal vocal fold volume and morphology.[5] Alternatively, injectable filler materials (e.g., carboxymethylcellulose and micronized collagen) may be used to augment the vocal folds for patients with glottic insufficiency secondary to loss of the SLP.[7] However, this treatment is temporary and fails to

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There are no financial incentives for the investigators, but the PRP tubes were donated by Eclipse.

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provide a durable effect.[8] In addition, it carries the risk of worsening dysphonia due to filler inert mass effect or superficially misplaced injection.[5]

For patients with vocal fold scar, a range of surgical procedures from augmentation laryngoplasty,[9] angiolytic laser procedures,[10] tissue grafting,[11] and Gray's mini-thyrotomy[12] have been described, which also provide inconsistent improvement.[13] Recent experimental studies have explored the prospect of restoring normal SLP architecture via stem cell tissue engineering[14] and growth factor injections.[15] Nevertheless, the paucity of controlled studies has left a void for a treatment modality that is safe, addresses the fundamental cause, and provides durable results for patients with vocal fold atrophy or scar.

Platelet-rich plasma (PRP) consists of platelets, growth factors, cytokines, and cell adhesion molecules derived from the patient's own blood.[16] PRP is believed to activate tissue regeneration by introducing high concentrations of platelet-derived growth factors and fibrin into damaged or atrophied tissue.[17] Studies in orthopedics and cosmetic surgery emphasize the breadth and safety of the therapeutic applications of PRP.[18–20] Previous work at our institution highlights the technical considerations for in-office PRP vocal fold injections.[21] Hence, serial PRP vocal fold injections hold promise as a new treatment modality for vocal fold atrophy and scar.

This study aims to evaluate the safety profile of autologous PRP for use as an injectable therapeutic in the vocal fold. Secondarily, we aim to determine the clinical efficacy of serial PRP vocal fold injections regarding patient-reported outcome measures and longevity of clinical effects from serial PRP vocal fold injections.

MATERIALS AND METHODS

Study Population

This study was approved by the University of Southern California Institutional Review Board. Patients were enrolled as part of an ongoing prospective clinical trial (clinicaltrials.gov APP-18-05224) consisting of a series of four unilateral vocal fold injections with autologous platelet-rich plasma. Vocal fold atrophy and lamina propria defects were diagnosed on laryngeal videostroboscopy by a fellowship-trained laryngologist. All participants were adults (age 18 years or older) with a baseline VHI-10 score ≥ 10. Patients with a history of allergy or hypersensitivity to lidocaine, amide-based anesthetics, or bovine products were excluded from the trial. Patients who underwent recent laryngeal surgery or invasive procedures (e.g., vocal fold injection augmentation) within the last 3 months were not permitted to enroll., Additionally, patients with active infection or inflammation in the larynx, underlying coagulopathy, thrombocytopenia, or platelet dysfunction, autoimmune disease, cancer, liver disease, or respiratory compromise were excluded. Concomitant laryngeal conditions including but not limited to vocal tremor and laryngeal dystonia that would otherwise warrant alternative interventions for optimal treatment were also excluded. Finally, patients with a life expectancy of less than 6 months were excluded from this study.

Clinical Protocol

The clinical protocol for this clinical trial is outlined in Figure 1. As part of the initial intake, patients completed the Voice Handicap Index-10 (VHI-10) and Vocal Fatigue Index (VFI). During their initial visit, a complete history and physical examination were performed along with voice and laryngeal videostroboscopy recordings. The first PRP vocal fold injection (Day 0) was performed within 4 weeks of the decision to participate. The patient was monitored for 1 h post procedure for any potential adverse events. The following day (Day 1), the patient was re-evaluated in clinic for any side effects or adverse events. One week following the initial injection the patient was re-evaluated in clinic and VHI-10 and VFI questionnaires were collected. Subsequently, the patient returned at monthly intervals for repeat evaluation and re-injection for a total of four unilateral vocal fold injections. The patient's subjective experience, patient-reported outcome measures, and stroboscopic examination were collected at each visit. Patients continued follow-up visits at monthly intervals for 3 months following the fourth injection (Fig. 2).

Drug/Device Information and Administration

The leukocyte poor platelet-rich plasma preparation was achieved via the Eclipse PRP® system manufactured by Eclipse Med. The Eclipse PRP® system is an FDA-cleared 510(k) Class II medical device (BK110035). Activation of PRP in our study is accomplished without exogenous substances by relying on shear force from injection and exposure to native collagen at the injection site.[18] Patients underwent venipuncture to collect 11 ml of blood. The collected blood was placed in the Eclipse PRP® system centrifuge per product protocol.

Study Agent Administration

Unilateral injection of 1.0–2.0 cc of PRP into the membranous vocal fold near the area of the scar on the pre-determined side was performed using a 23-gauge needle via previously described percutaneous methods for vocal fold injection (thyrohyoid, transoral approaches).[8] Trans-cervical injections were carried out through the thyro-hyoid approach with no significant leakage of PRP noted during these injections. Injections were performed throughout this study taking care to place the needle superficially into the vocal fold. The PRP then tracks throughout the entire surface of the superficial vocal fold and bulges the epithelium. Once material begins to extrude, commonly between 1 and 1.5 cc, the injection is concluded. All injections were performed in an outpatient clinic setting under local and topical anesthesia apart from one patient who requested injection 2 be performed in the operating room due to intolerance of awake in-office vocal fold injection. Due to this patient's preference, accommodations were made to perform injections 3 and 4 in the operating room as well. The contralateral vocal fold did not undergo injection and served as an internal control. During interim periods between scheduled visits, subjects were instructed to call with any potential adverse event that may require in-person evaluation at the clinic or in an acute care setting for appropriate clinical care.

Evaluation Criteria and Endpoint Definitions

Study completion was achieved after patients received four unilateral PRP injections and completed all follow-up post-injection clinic visits. The main objective of this study is to define the safety profile of PRP for use with serial vocal fold injections to treat vocal fold atrophy and scar. As such, the focus will be on any

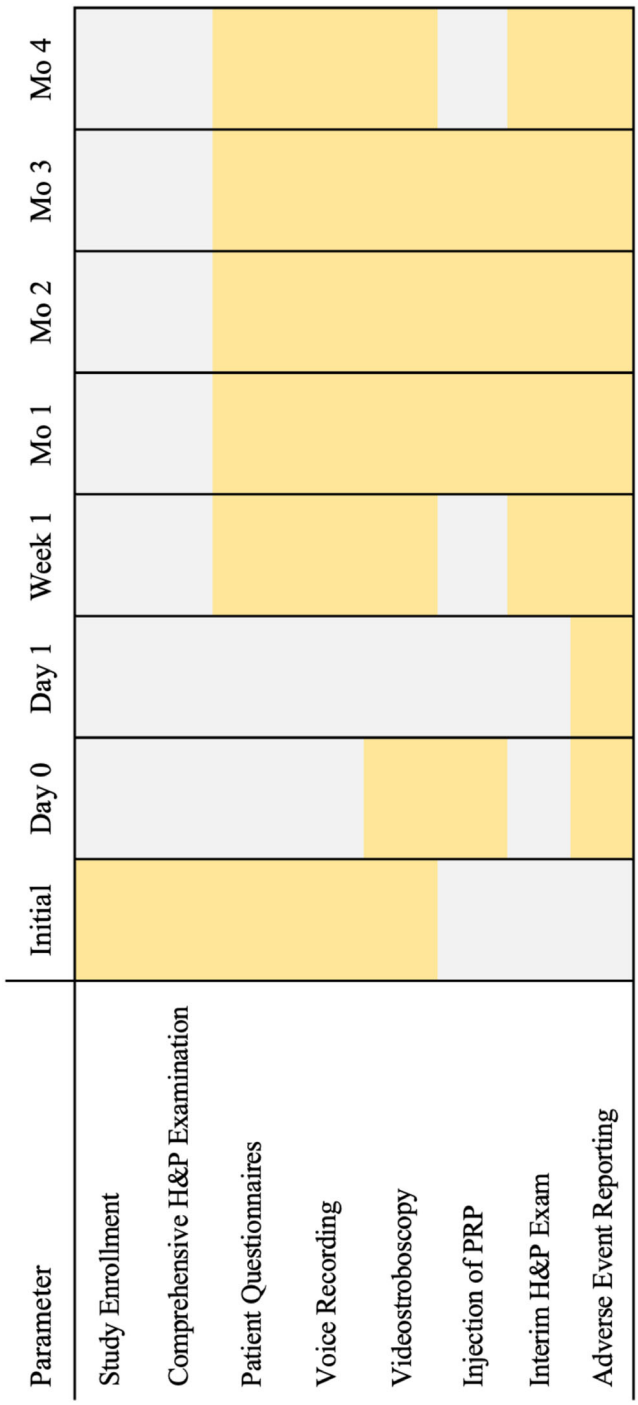

Fig. 1. Clinical vvaluation and study calendar. This calendar sequentially outlines every evaluation and intervention performed along various study timepoints. Initial, designates the first clinic visit during which patients are enrolled in the study. Day 0, designates the day patients receive the first vocal fold injection with PRP, which may be the same day as Initial for some. Subsequent day, week, and month designations are relative to Day 0 of injection. H&P = History and Physical; Mo = Month; PRP = Platelet-Rich Plasma. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

treatment-related adverse events that are reported during the study. Previously cited adverse events in vocal fold injection include local tissue reactivity, hemorrhage, hematoma, granuloma formation, and postprocedural airway compromise.[22] Secondary endpoints included patient-reported outcome measures (VHI-10, VFI) from designated follow-up time points which are compared to baseline values prior to the first injection. Follow-up duration refers to the number of months since a patient's first injection and continues to accumulate after all four injections have been administered. For patients with vocal fold scars, we did not include specific etiology in our demographic information as many patients had longstanding scars of unknown etiology.

Statistical Analysis

Sample size calculations were performed based on data from prior studies for VHI-10 outcomes after vocal fold augmentation for vocal fold atrophy.[23] These calculations were based on a planned comparison of VHI-10 scores before and after serial PRP injections via paired t-test statistics. All comparisons were made between baseline scores and individual post-injection timepoint. The primary outcome of safety was focused on the incidence of serious adverse events related to the study material under investigation. We expected the risk of a serious adverse event to be exceedingly low and did not base our sample size calculation on that. The study cohort will be analyzed using descriptive statistics of the primary outcome. The incidence of both minor and major adverse events will be measured as a percent of total participants experiencing said adverse event. Comparison of patient-reported outcome measures from post-intervention time points to pre-intervention baseline were evaluated using parametric statistics (t-test, paired two samples for means, two-tail).

RESULTS

Twelve patients with vocal fold scar or atrophy underwent unilateral vocal fold injection with autologous PRP prepared according to Eclipse PRP® system protocol. A total of 43 injections were performed using a peroral or percutaneous approach. An overview of study participant demographics and pathology is outlined in Table I. An average of 1.57 ± 0.4 cc (range 0.6–2.0 cc) of injectate was used. The average duration of follow-up was 3.6 ± 1.8 months. Nine patients (75.0%) completed all four PRP injections, while two patients completed three injections and one patient received only one injection as part of the ongoing trial. At the one-month timepoint, one patient requested to receive the PRP injection in the operating room to better tolerate treatment. All other injections were performed in the outpatient clinic setting. No significant inflammatory reactions or adverse events were seen to date.

Patient-reported outcome measures using the VHI-10 and VFI questionnaire scores taken at every study evaluation timepoint are reported in Table II. The VHI-10 and VFI scores reflect study participant baseline values, 1 week after initial PRP treatment, and every subsequent treatment timepoint in the trial. The average VHI-10 and VFI scores at baseline were 29.7 ± 9 and 45.9 ± 16.8, respectively. At 1 week after the first PRP injection the average VHI-10 and VFI scores began to downtrend to 27.5 ± 10.2 and 42.9 ± 16.4. At the one-month timepoint, the average VHI-10 score of 24.1 ± 10.6 (median ΔVHI-10 = 4.4, $p = 0.02$) and average VFI score was 32.1 ± 185 (mean ΔVFI = 12.8, $p = 0.04$) reflected

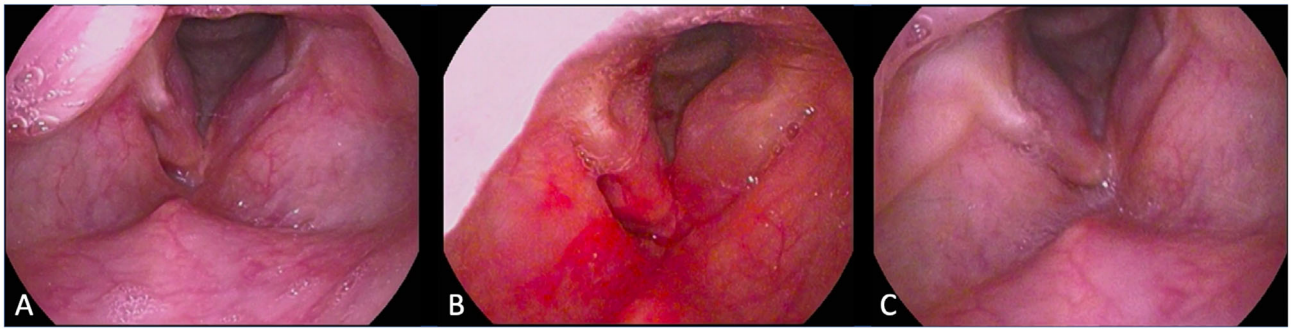

Fig. 2. In-office Laryngoscopy photos. (A) Pre-injection (B) Post-PRP injection (C) 1 month post-injection. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

TABLE I.
Study Participant Demographic and Pathology Overview.

Case	Age	Sex	Pathology	Prior Treatment	Side of Injection	Number of Injections	Average Injectate (Range cc)	Average Follow-up Time (Months)
1	74	M	Vocal fold scar and atrophy	Thyroplasty revision, voice therapy	Left	4	1.6 (1.5–2.0)	6
2	50	M	Vocal fold scar	Steroid, injectable filler, voice therapy	Right	4	1.8 (1.5–2.0)	6
3	49	F	Vocal fold scar	Voice therapy	Right	4	1.8 (1.5–2.0)	3
4	81	F	Vocal fold scar	Injectable filler, Fat Implantation	Right	4	1.8 (1.5–2.0)	5
5	62	M	Vocal fold scar	Thyroplasty Revision, Voice Therapy	Left	4	2.0 (2.0)	6
6	66	M	Vocal fold atrophy	Voice therapy	Left	4	1.0 (1.0)	4
7	61	M	Vocal fold scar	Thyroplasty revision, voice therapy	Left	3	2.0 (2.0)	2
8	64	M	Vocal fold scar	Dupixent, diflucan, voice therapy	Left	3	1.5 (1.5)	1
9	63	M	Vocal fold scar	Autologous stem cell transplant	Left	4	1.5 (1.0–2.0)	3
10	79	F	Bilateral vocal fold scar	Injectable filler, voice therapy	Left	4	1.3 (1.0–2.0)	3
11	44	M	Bilateral Vocal fold scar	Steroid and injectable filler	Left	4	1.0 (0.6–1.5)	3
12	45	M	Bilateral vocal fold scar	Injectable filler, voice therapy	Right	1	1.2 (1.2)	1

F = Female; M = Male.

TABLE II.
Patient-Reported Outcome Measures after Serial Vocal fold PRP Injections.

Parameter	Baseline	1 Week After 1st Injection	1 Month (2nd injection)	2 Month (3rd Injection)	3 Month (4th Injection)	4 Month
Patients (*n*)	12	11	10	10	9	5
VHI-10	29.7 ± 9	27.5 ± 10.2 (0.12)	24.1 ± 10.67 (0.02)*	19.9 ± 11.3 (0.005)*	18.9 ± 12.4 (<0.001)*	16.4 ± 14.8 (0.03)*
VFI	45.9 ± 16.8	42.9 ± 16.4 (0.9)	32.1 ± 18.5 (0.04)*	31.1 ± 14.9 (0.04)*	25.1 ± 16.2 (0.01)*	14.4 ± 11.8 (0.08)

VFI = voice fatigue index; VHI-10 = voice handicap index-10.
*Indicates statistical significance as determined by 2-tailed paired *t*-test. All comparisons were made between baseline scores and individual post-injection timepoint.

the earliest significantly significant decrease in both questionnaires. This significant downtrend persisted through the two-month (VHI-10 score 19.9 ± 11.3; VFI 31.1 ± 14.9) and three-month (VHI-10 18.9 ± 12.4; VFI 25.1 ± 16.2) timepoints. At the four-month timepoint, one month after the fourth injection, the VHI-10 score was 16.4 ± 14.8 (median ΔVHI-10 = 8.4, $p = 0.03$) and the VFI score was 14.4 ± 11.8 (mean ΔVFI = 23.8, $p = 0.08$).

All patients self-reported tolerating the procedure without difficulty or immediate complications. Some patients described discomfort associated with the laryngotracheal anesthetic and mild discomfort was noted

on the side of injection in two patients 1 day after the initial injection. No safety events were reported from any of the injections ($n = 43$) throughout the duration of the trial.

All patients continued to experience subjectively improved voice outcomes, with the improved overall quality, loudness, vocal endurance, and less strain and breathiness at 1 month. Two patients noted that the improvements were sustained until 3 weeks following the first injection when they experienced a slight deterioration but did not return to their baseline dysphonia. Eight patients continued to experience improved voice quality and resonance 1 month following the second injection. Two patients reported sustained voice quality at the level experienced after the initial injection with no notable improvement thereafter. All patients reported subjective improvement in their voice 1 month after the third injection, of which three experienced their best overall voice enhancement. Two patients consistently experienced gradual deterioration in their voice quality and noted voice instability as they neared the one-month timepoint following each injection.

DISCUSSION

While the application of regenerative medicine techniques in laryngology holds great promise there is a paucity of human data on the use of PRP. This prospective cohort study demonstrated a favorable safety profile for the use of serial in-office vocal fold injections of autologous PRP among patients with vocal disturbances due to vocal fold atrophy and scar. There were no adverse events or peri-procedural complications across 43 PRP injections in 12 patients. The practicality of in-office procedures has been embraced in laryngology as they circumvent the use of general anesthesia and the need for an operating room and staff.[24,25] The bioactive components in PRP such as growth factors, cytokines, and cell adhesion molecules are self-renewing. Moreover, the plasma derivative tissue product is reliably reproduced via routine blood draws and minimal subsequent manipulation. In this trial, blood collection and centrifugation added approximately 10–15 min of preparation time. Blood collection, PRP product preparation, and treatment can be completed in a timely manner rendering the process feasible for the ambulatory care setting.

Lamina propria defects found in vocal fold atrophy and scar represent challenging pathologies to treat.[3] Therapeutic interventions include surgical and non-surgical options including tissue transplantation, angiolytic laser treatments, and voice therapy. Surgeons must consider the diverse roles of the larynx during respiration, phonation, and deglutination[26,27] to preserve functional capacity following treatment.[2,28] Pathologic healing from scar tissue can lead to persistent dysphonia that impairs appropriate vocal fold approximation and natural dynamic oscillation required for clear resonant voice sounds.[3] Moreover, there is no substance to replace the intricate framework of the SLP. Prior to trial enrollment, all patients underwent some form of previous treatment including steroid injections, injection augmentation, or surgical scar revision. Despite these interventions, these patients continued to have residual vocal deficits despite temporary improvement seen in some instances. All participants expressed dissatisfaction with their vocal capabilities during the baseline evaluation.

PRP is a biological material shown to stimulate host tissue rejuvenation without eliciting immune rejection as it is derived from the patient's own blood. The composition of PRP consists primarily of a high concentration of platelets and growth factors but can also include white blood cells and other vasoactive and chemotactic agents.[29] PRP releases growth factors that expedite wound healing via cell proliferation, matrix formation, osteoid production, connective tissue healing, angiogenesis, and collagen synthesis.[30,31] PRP injections have been shown to have a broad range of applications in tissue sealing, stabilization, scar maturation, osteogenesis, and alopecia across various surgical specialties from orthopedics to cosmetic surgery with virtually no adverse side effects.[32–34] In vivo studies revealed the effect of PRP in vocal fold healing in rabbit models following acute vocal fold injury.[29] In otolaryngology, the wound healing properties of PRP have previously been used to treat tympanic membrane perforation.[35] This prospective clinical report on the use of PRP in the human larynx is unique and builds on recent interest in commissioning bioactive components, including fibroblast growth factors and autologous bone marrow-derived mesenchymal stromal cells, to treat pathologies of the head and neck. Recently Woo et al. reported short-term voice improvements following inoffice PRP injections with 11 patients receiving three injections.[26] While our preliminary work set out to show the safety and tolerability of PRP injections in an ambulatory care setting, many of the patients expressed subjective improvements occurring after a four-injection series. The standardized design of our prospective trial, formatted with consistent follow-up after four unilateral vocal fold injections, provides a unique and controlled study method. As a newly emerging therapeutic avenue in laryngology, our findings contribute to the scarcity of literature exploring the potential use of PRP injections as a suitable treatment modality for patients with vocal fold scar and atrophy. Our results are consistent with the safety of PRP injections described by Woo et al., and further support the use of PRP precisely because of their similarity.

All patients underwent treatment without difficulty or complications. There were no accounts of laryngeal edema, local inflammatory reaction, dysphagia, or dyspnea. Mild discomfort was noted on the side of injection in two patients 1 day after the initial injection. Patients in our trial expressed a variable range of voice improvement. Three patients described a mild roughness in the quality of their voice for 3–5 days following the first injection which subsequently resolved. One patient went on to experience a similar occurrence at their second injection. Patient experiences reflected a general trend of improvement with consecutive PRP injections. Three accounts across two patients described sustained improvement for 3 weeks following treatment before perceiving remission in voice quality. Generally, patients experienced vocal

quality and consistency that eventually spanned the month between injections. Interestingly, three subjects experienced their best overall voice improvement after injection number three. All patients who received four PRP injections were satisfied with the improvement of their voice and expressed interest in continued treatment beyond the completion of their trial participation.

VHI-10 and VFI scores mirror the trend of gradual improvement. At 1 week after the first PRP injection, the average VHI-10 and VFI scores began to downtrend to 27.5 ± 10.2 and 42.9 ± 16.4 but did not achieve the range of published minimally important clinical difference (MCID) for either questionnaire.[36,37] However, by 1 month, the change in the average VHI-10 and VFI scores reflected a significant decrease compared to baseline, beyond the MCID range of a four-to-six-point decrease in total score. With repeat monthly injections both the average VHI-10 and VFI scores continued to decrease significantly with subsequent follow-up evaluations at the two and three-month timepoints. Interestingly, at the four-month timepoint, both the VHI-10 and VFI scores continued to decrease, but only the VHI-10 score was significantly lower than baseline. It is important to note that only five patients have reached this point in the study. Therefore, it is perhaps too early to comment on the longevity of serial PRP injections in terms of their impact on these patient-reported outcomes.

Our preliminary work contains encouraging outcome trends that may point to positive outcome longevity regarding voice quality in patients treated with serial PRP injections. Continued patient follow-up and enrollment will further elucidate the therapeutic role of PRP in laryngology. Determining the safety of PRP treatment is a crucial step toward characterizing its use in patient care with respect to outpatient laryngeal procedures. While this work builds on earlier efforts from our institution outlining the technical feasibility and safety of PRP injections, ongoing enrollment will continue to substantiate our early findings.[21] While the contralateral vocal fold served as a control, incorporating a volume-occupying control such as saline or platelet-poor plasma could be beneficial in definitively attributing vocal improvements to the bioactive components in PRP.

The trial contains clear limitations. The subjective nature of patient-reported voice outcomes limits the scope of meaningful conclusions about the procedure's long-term efficacy. To that end, patient experiences need to be correlated to objective anatomical changes and voice parameters. By the current trial design, patients will be followed-up for a minimum of 12 months after the concluding injection. Future work will assess objective outcome measurement from video stroboscopic evaluation which will provide a functional clinical correlate to bolster the results thus far. More work is also needed to determine the optimal timing of PRP treatment and the number of injections needed to provide optimal effect.

CONCLUSION

The absence of any reported safety events during the application and follow-up period for 43 unilateral vocal fold injections using PRP indicates its safety for use in the ambulatory care setting. The standardized approach of PRP preparation and application to the vocal folds represents a safe therapeutic approach for patients with vocal fold atrophy or scar. Subjective improvements in vocal quality were accompanied by significant decreases in VHI-10 and VFI questionnaire scores in patients included in this trial. The overall trend of the patient-reported outcome measures indicates voice improvements beyond the limits of the MCID for these measures. While these results persisted for most patients during the trial, a few did report a gradual decline in voice quality after receiving a PRP injection. Additional follow-up will determine the true longevity and extent to which in-office PRP injections affect objective voice parameters. Ongoing enrollment in the clinical trial will continue to assess the safety and therapeutic benefits of serial PRP injections.

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