ORIGINAL RESEARCH

Long-term results and safety of fibroblast growth factor injection for unilateral vocal fold paralysis

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Abstract

Objectives: Treatments for unilateral vocal fold paralysis (UVFP) include conservative voice rehabilitation, vocal fold injection, and laryngeal framework surgery. We proposed basic fibroblast growth factor (bFGF) injection as a potential novel treatment for UVFP and have reported the short-term results. In this study, we present the long-term results and safety of vocal fold bFGF injection as a treatment for UVFP.

Methods: This retrospective study included 42 patients (25 males and 17 females) with UVFP who were administered a local injection of bFGF. The injection regimen involved injecting FGF (0.5 μg/ml in 0.5 ml per side) into the bilateral vocal folds using a 23-gauge injection needle. Phonological outcomes were evaluated 6 months and 12 months after the injection.

Results: Overall, 26 patients received a single injection of bFGF, six patients received an additional injection, and 10 patients received the additional framework surgery. Maximum phonation time, mean flow rate, pitch range, jitter and shimmer percentages, the total GRBAS (grade, roughness, breathiness, asthenia, strain) score, and voice handicap index scores improved significantly in the long term. In patients who received the additional injection or framework surgery, the effects of bFGF injection were temporary, but did not interfere with the performance of the framework surgery.

Conclusion: In total, 42 patients who underwent vocal fold bFGF injections were reviewed. The bFGF injections were effective and safe in the long-term results for UVFP in the selected cases. Some patients with severe symptoms benefited from the additional framework surgery but not the additional bFGF injection.

KEYWORDS
basic fibroblast growth factor, long-term results, unilateral vocal fold paralysis, vocal fold injection therapy

1 | INTRODUCTION

Unilateral vocal fold paralysis (UVFP) occurs due to various reasons, including surgical, neoplastic, idiopathic, traumatic, central, and cardiovascular causes.[1] The main symptoms of UVFP include dysphonia[2] and dysphagia,[3] which greatly affect the quality of life of patients and require effective treatment for recovery. Various treatments have been proposed for UVFP, including conservative treatments such as voice hygiene, voice rehabilitation, and medication.[4] However, these have not been established as standard treatments. In severe cases, laryngeal framework surgery techniques such as thyroplasty type I and/or arytenoid adduction[5] have shown good results. However, this surgery has some limitations, including the need for a neck incision and several days of hospitalization.[5] In addition, reoperation poses difficulties in cases in which the original surgery was not sufficiently effective.[6]

Patients with mild symptoms who do not qualify for this highly invasive surgery require certain treatments. Treatments are also required for patients to maintain an acceptable quality of life during the waiting period of 6 months before the surgery. Previously, such patients were treated mainly with injections of fat,[7] non-crosslinked bovine collagen,[8] and calcium phosphate cement.[9] Since 2014, we have been administering basic fibroblast growth factor (bFGF) injections to the vocal fold for various vocal fold lesions.[10] The main advantage of bFGF injection is that it stimulates the fibroblasts in the vocal folds to restore their preferable structure without the introduction of foreign materials.

Recent advances in molecular biological research have popularized tissue engineering techniques using growth factors, cells, and scaffolding.[11] The delivery of external growth factors is a simple method that has been attempted in several fields.[12] In particular, bFGF—one of the major growth factors—has been used to treat vocal fold lesions.[10,13–16] bFGF injection stimulates the hyaluronic acid production and inhibits collagen production by proliferating the reduced fibroblasts in the superficial lamina propria (SLP) of atrophic vocal folds. This increases the thickness of the SLP, thereby improving the symptoms of dysphonia caused by vocal atrophy and sulcus vocalis.[15,17–19] However, bFGF injection was most effective in prolonging the MPT of UVFP compared with other disease indicating that UVFP could be suitably treated with bFGF injections.[10] A sex-specific study on UVFP also demonstrated that bFGF injection improved MPT, mean airflow rate (MFR), and pitch range (PR) in patients, regardless of sex.[14] In this study, we investigated whether bFGF injection can be used as a standard therapeutic strategy for UVFP by examining the long-term results and safety of bFGF injections and its indications in UVFP patients.

2 | MATERIALS AND METHODS

2.1 | Study participants

This retrospective cohort study was approved by the Institutional Review Board of the International University of Health and Welfare, Tokyo Voice Center, Japan (14-S-3). Before injection, written informed consent was obtained from all patients. We included 42 patients (25 men and 17 women) who had undergone bFGF injection at the International University of Health and Welfare from December 2015 to November 2017 and had been followed up for >1 year (12 months). The mean age of the patients was 64.4 years (range, 38–94 years). In 33 cases, UVFP was caused by thoracic aortic aneurysm, thyroid cancer, lung cancer, esophageal cancer, mediastinal tumor, and their associated surgeries. UVFP was idiopathic in nine cases. All patients had experienced persistent dysphonia due to UVFP for >6 months, were dissatisfied with voice rehabilitation, were offered both laryngeal framework surgery and bFGF injection, and had chosen bFGF injection. Patients with severe aspiration and those who had already undergone laryngeal framework surgery were excluded. In all cases, the injection was administered bilaterally. The medical records of all patients were reviewed, and the laryngeal findings were confirmed by two or more independent phonosurgeons or speech-language-hearing therapists.

2.2 | Injection procedure

The injection was administered as described previously.[10,14] Briefly, local anesthesia was administered (4% lidocaine sprayed on the pharynx and larynx). Following this, bFGF (Fiblast; Kaken Pharmaceutical Company Ltd.) was injected into the bilateral vocal fold (0.5 μg/ml; 0.5 ml per side) using a Varixar 23G needle (TOP Corp.) inserted into the treatment channel of the flexible laryngeal fiber. One hour after the injection, the laryngeal findings were examined to find any acute adverse effects. The patients were requested to maintain voice rest on the day of the injection and the following day. According to the findings in our preliminary study, which suggested that bFGF injection into the bilateral vocal folds can yield more favorable outcomes than unilateral injection, even in UVFP, all included cases received bilateral injections.

2.3 | Voice laboratory measurements

Voice laboratory measurements included MPT, MFR, PR, speech fundamental frequency (SFF), jitter, shimmer, noise-to-harmonic ratio (NHR), the total GRBAS (grade, roughness, breathiness, asthenia, strain) score (tGRBAS; the sum of the scores on the GRBAS scale), and the voice handicap index (VHI). The measurements were recorded before the bFGF injection and 6 months (6M) and >12 months (12M) after the bFGF injection. MFR was measured using the Phonatory Function Analyzer (PS-77E; Nagashima Medical Instruments Company Ltd.). Jitter, shimmer, SFF, and NHR were measured using a computerized speech lab device (Model 4500, KayPENTAX). PR was measured objectively using an electronic piano keyboard.

2.4 | Statistical analysis

In the single-injection group, the changes in voice laboratory measurements were tested using one-way ANOVA. A *p* value of <.005 was
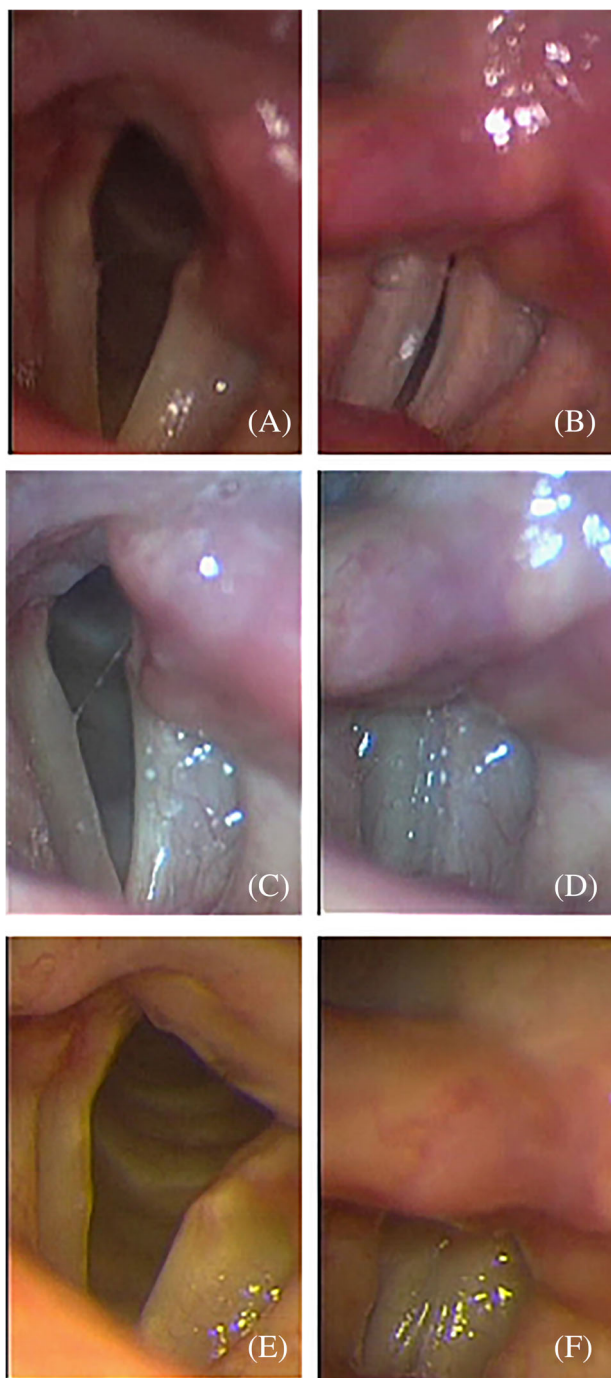
FIGURE 1 Stroboscopic vocal fold examination of a representative patient with UVFP. (A) Inspiratory phase at pre-injection. (B) Phonation phase at pre-injection. (C) Inspiratory phase at 6 months post-injection. (D) Phonation phase at 6 months post-injection. (E) Inspiratory phase at 12 months post-injection. (F) Phonation phase at 12 months post-injection. UVFP, unilateral vocal fold paralysis.

considered statistically significant to account for the Bonferroni correction and avoid multiple comparison problems. The measured parameters in the single-injection and additional treatment groups were also compared using Welch's *t* test.

3 | RESULTS

3.1 | Adverse events

As in previous reports, no allergic reactions or serious adverse effects were observed in the present study. Some patients experienced severe hoarseness associated with transient hyperemia, which resolved completely after 2–3 weeks of follow-up. Although there were concerns about atrophy and defective granulation in the vocal folds as long-term results, no such reactions were observed.

3.2 | Representative cases

Figure 1 and Video S1 show the stroboscopic findings of the larynx in a typical case. The patient was a 72-year-old male who had severe hoarseness due to UVFP caused by a thoracic aortic aneurysm. His MPT was 10 s, and the GRBAS score was 22100. At the pre-injection stage, the inspiratory and phonation phases of the vocal fold (Figure 1A,B) showed severe glottal closure and suppression of vibration during vocalization. At 6 months after the injection (Figure 1C,D), the glottal gap during vocalization had decreased, and the vibrations of the paralyzed vocal folds had recovered. These findings were maintained at 12 months after the injection (Figure 1E,F). MPT improved to 13 s at 6 months post-injection and 20.5 s at 12 months post-injection. Pre-injection showed elliptical closure, with contact at vocal process, and 12 months post-injection showed slight left vocal fold motion; however, this motion recovery had not been demonstrated in most cases.

As in the representative patient, most patients improved in voice laboratory measurements and stroboscopic findings in the single-injection group.

3.3 | Clinical course after the initial injection

At the 12-month follow-up after the initial injection, 26 patients received no additional treatment (the single-injection group), six received additional injections because of the diminished efficacy of the first injection (the additional injection group), and 10 underwent additional laryngeal framework surgery after injection (the additional framework surgery group). Among these 10 patients, the post-operation results of four patients were not recorded.

3.4 | Voice laboratory measurements for the single-injection group

3.4.1 | Aerodynamic and acoustic analyses

Compared with the pre-injection values, MPT increased in 24 (of 26) patients at 6 months post-injection and in 23 (of 26) patients at
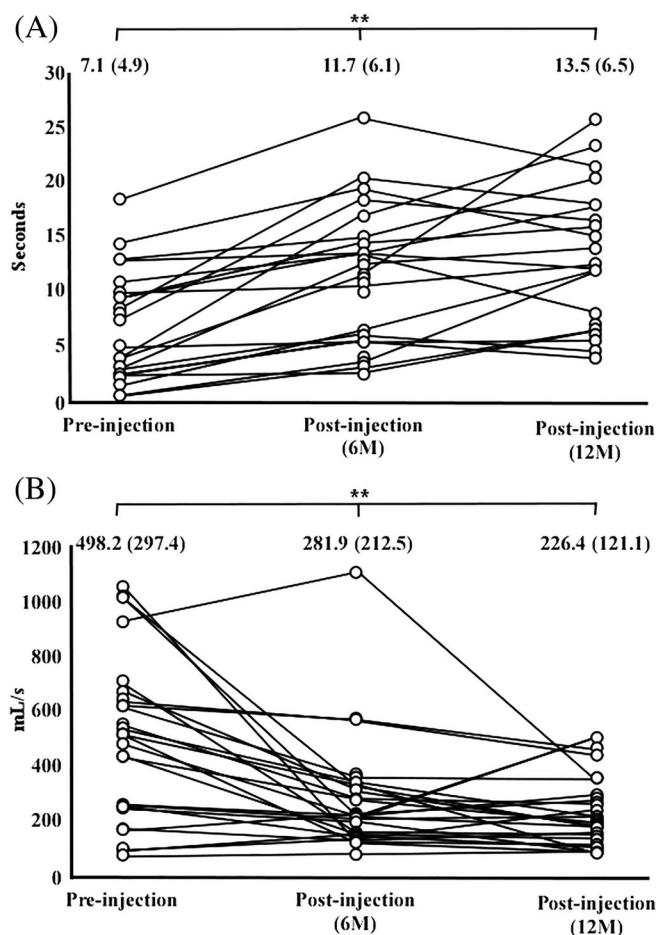
(A)

(B)

FIGURE 2 Changes in the maximum phonation time and mean airflow rate in the single-injection group. (A) Maximum phonation time at pre-injection and at 6 months and 12 months post-injection. (B) Mean airflow rate at pre-injection and at 6 months and 12 months post-injection. The values of mean and standard deviation at pre-injection, 6-month post-injection, and 12-month post-injection are listed in graphs as mean (SD). Significant differences are determined by one-way ANOVA. **$p < .005$.

(A)

(B)

FIGURE 3 Changes in pitch range and speech fundamental frequency in the single-injection group. (A) Pitch range at pre-injection and at 6 months and 12 months post-injection. (B) Speech fundamental frequency at pre-injection and at 6 months and 12 months post-injection. The values of mean and standard deviation at pre-injection, 6-month post-injection, and 12-month post-injection are listed in graphs as mean (SD). Significant differences are determined by one-way ANOVA. **$p < .005$. n.s., no significant difference; ST, semitone.

12 months post-injection. The mean MPT increased significantly from 7.1 s (standard deviation [SD], 4.9 s) at pre-injection to 11.7 s (SD, 6.1 s) at 6 months post-injection and 13.5 s (SD, 6.5 s) at 12 months post-injection (Figure 2A) ($p < .005$). MFR was reduced in 20 of the 26 patients at 6 months post-injection and in 18 of the 26 patients at 12 months post-injection (compared with the pre-injection values). Compared with the pre-injection mean MFR of 498.2 ml/s (SD, 297.4 ml/s), the MFR values decreased significantly to 281.9 ml/s (SD, 212.5 ml/s) at 6 months post-injection and 226.4 ml/s (SD, 121.1 ml/s) at 12 months post-injection (Figure 2B) ($p < .005$). PR increased in 20 (of 26) patients at 6 months post-injection and 21 (of 25) patients at 12 months post-injection (compared with the pre-injection values). The mean PR increased significantly from 17.3 semitone (SD, 10.7 semitone) at pre-injection to 23.8 semitone (SD, 9.3 Semitone) at 6 months post-injection and 27.9 semitone (SD, 9.6 semitone) at 12 months post-injection (Figure 3A) ($p < .005$).
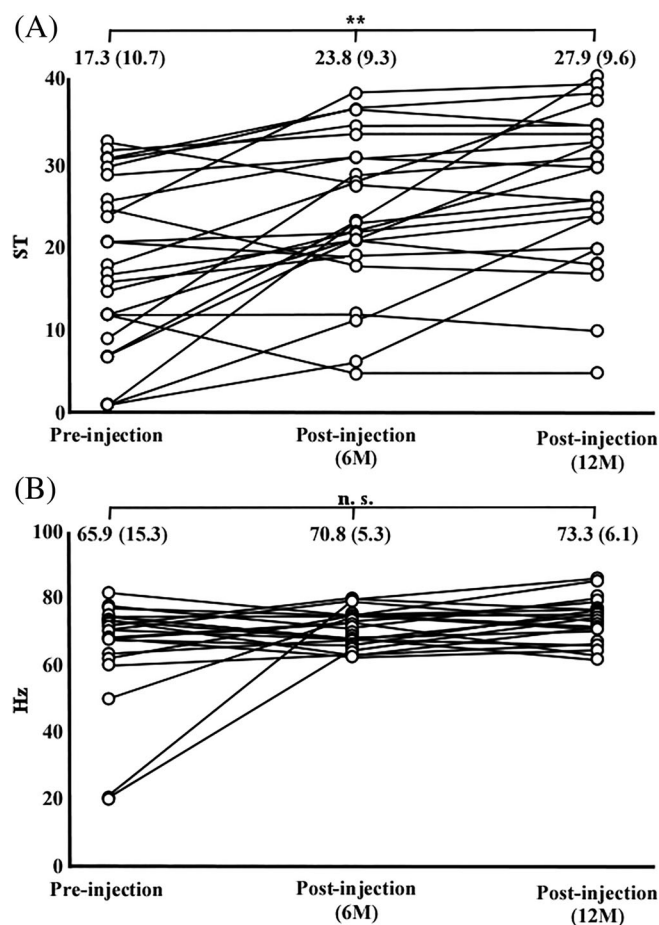
Compared with the pre-injection values, SFF increased in 14 (of 26) patients and decreased in 11 (of 25) patients at 6 months post-injection, and increased in 18 (of 25) patients and decreased in seven (of 25) patients at 12 months post-injection. The pre-injection mean SFF of 65.9 Hz (SD, 15.3 Hz) increased to 70.8 Hz (SD, 5.3 Hz) at 6 months post-injection and 73.3 Hz (SD, 6.1 Hz) at 12 months post-injection. However, the mean SFF values were not significantly different (Figure 3B). Compared with the pre-injection values, jitter decreased in 15 (of 21) patients at 6 months post-injection and 13 (of 21) patients at 12 months post-injection. The mean jitter decreased significantly from 4.5% (SD, 3.7%) at pre-injection to 2.0% (SD, 1.5%) at 6 months post-injection and 1.3% (SD, 1.3%) at 12 months post-injection (Figure 4A) ($p < .005$). Compared with the pre-injection values, shimmer decreased in 17 (of 21) patients at 6 months post-injection and 13 (of 21) patients at 12 months post-injection. The mean shimmer decreased significantly from 9.4% (SD,
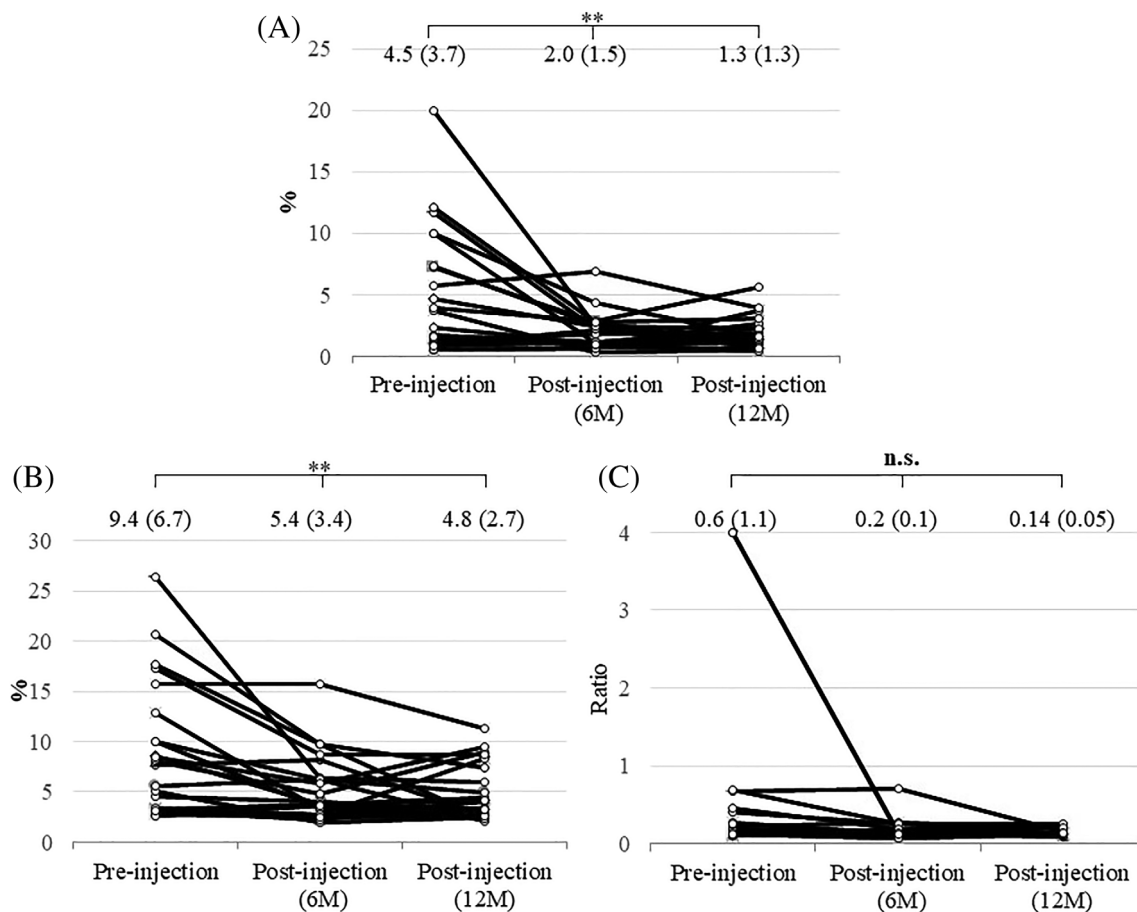
FIGURE 4 Changes in jitter percentage, shimmer percentage, and noise-to-harmonic ratio in the single-injection group. (A) Jitter percentage at pre-injection and at 6 months and 12 months post-injection. (B) Shimmer percentage at pre-injection and at 6 months and 12 months post-injection. (C) Noise-to-harmonic ratio at pre-injection and at 6 months and 12 months post-injection. The values of mean and standard deviation at pre-injection, 6-month post-injection, and 12-month post-injection are listed in graphs as mean (SD). Significant differences are determined by one-way ANOVA. **$p < .005$. n.s., no significant difference.

6.7%) at pre-injection to 5.4% (SD, 3.4%) at 6 months post-injection and 4.8% (SD, 2.7%) at 12 months post-injection (Figure 4B) ($p < .005$). Compared with the pre-injection values, NHR decreased in 14 (of 21) patients at 6 months post-injection and 16 (of 21) patients at 12 months post-injection. However, the mean NHR values were not significantly different (Figure 4C).

3.4.2 | tGRBAS score

The GRBAS scale is widely used for the perceptual evaluation of voice quality. Compared with the pre-injection scores, the tGRBAS scores decreased in 20 (of 23) patients at 6 months post-injection and in 20 (of 23) patients at 12 months post-injection. The mean tGRBAS score decreased significantly from 4.8 (SD, 2.4) at pre-injection to 2.9 (SD, 2.9) at 6 months post-injection and 2.6 (SD, 1.9) at 12 months post-injection (Figure 5A) ($p < .005$).

3.4.3 | Voice handicap index

Compared with the pre-injection values, VHI decreased in 17 (of 21) patients at 6 months post-injection and 13 (of 21) patients at 12 months post-injection. The mean VHI decreased significantly from 44.6 (SD, 23.4) at pre-injection to 19.6 (SD, 17.4) at 6 months post-injection and 15.1 (SD, 16.8) at 12 months post-injection (Figure 5B) ($p < .005$).

3.5 | Predictive factors for additional treatment

During the 12-month follow-up period after the initial injection, six patients received additional injections because of insufficient effects, whereas 10 patients underwent additional laryngeal framework surgery. The patients who received additional injections showed significant improvements in MPT and MFR, although the effect was temporary and lasted only 3 months. In patients who underwent
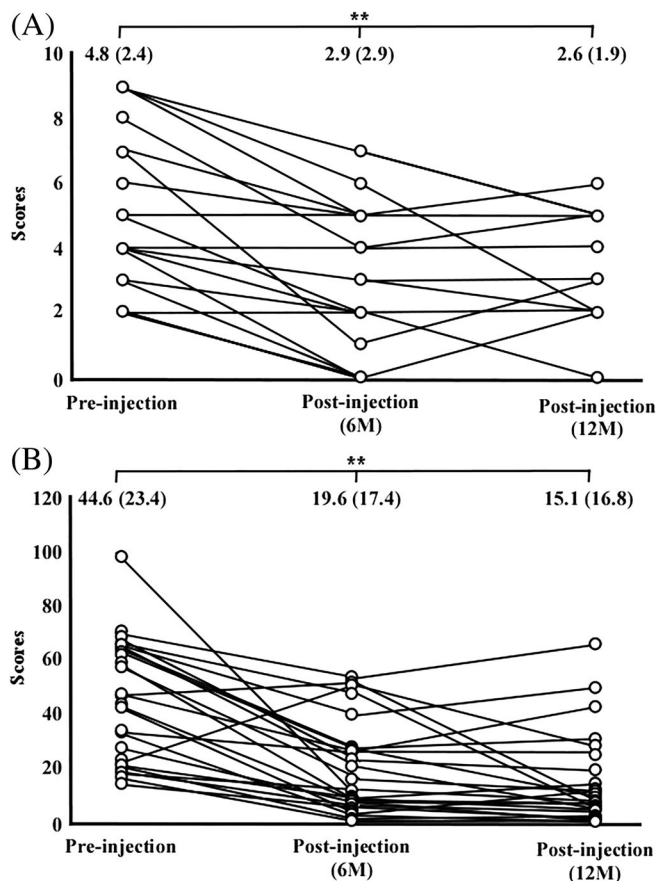
FIGURE 5 Changes in the total GRBAS (grade, roughness, breathiness, asthenia, strain) score and voice handicap index scores in the single-injection group. (A) Total GRBAS score at pre-injection and at 6 months and 12 months post-injection. (B) Voice handicap index scores at pre-injection and at 6 months and 12 months post-injection. The values of mean and standard deviation at pre-injection, 6-month post-injection, and 12-month post-injection are listed in graphs as mean (SD). Significant differences are determined by one-way ANOVA. **$p < .005$.

TABLE 1 Differences in parameters between the single-injection and additional treatment groups.

Parameters	Single injection	Additional treatment	p values
Sex (M:F)	15:11	10:6	.4260
Age (years)	61.8 (12.6)	68.4 (14.2)	.1320
MPT (s)	7.1 (4.8)	4.2 (3.18)	.049*
MFR (ml/s)	498.3 (297.3)	679.2 (346.2)	.0820
SFF (Hz)	65.9 (15.3)	68.2 (7.9)	.5770
Jitter (%)	5.2 (5.1)	5.8 (3.9)	.6860
Shimmer (%)	9.4 (6.7)	10.7 (7.4)	.5850
NHR	4.4 (2.7)	6.4 (1.9)	.012*
VHI	44.6 (23.4)	55.8 (20.3)	.1230
tGRBAS	4.4 (2.7)	6.2 (1.8)	.049*

Note: Values shown are mean (standard deviation).
Abbreviations: MFR, mean airflow rate; MPT, maximum phonation time; NHR, noise-to-harmonic ratio; SFF, speech fundamental frequency; tGRBAS, total GRBAS (grade, roughness, breathiness, asthenia, strain) score; VHI, voice handicap index.

4 | DISCUSSION

UVFP can be caused by various conditions—including thoracic aortic aneurysm, esophageal cancer, lung cancer, mediastinal tumor, and thyroid cancer—their related surgeries, and viral diseases. UVFP often impairs the quality of life by causing severe hoarseness and aspiration.[2,5] The proposed treatments for UVFP include conservative therapies—such as voice rehabilitation, voice hygiene,[4] and vocal fold injection using various materials[7–9]—and framework surgery, including medialization laryngoplasty and arytenoid adduction.[5,20] Among these, framework surgery appears to be the most effective. However, it may be unsuitable for patients in poor general condition due to uncontrolled disease and/or a recent highly invasive surgery. Therefore, it is important to develop a novel, minimally invasive, and effective treatment for UVFP and establish its indications. In our earlier work, we proposed bFGF injection as a potential novel treatment for UVFP.[14]

Using bFGF injections to treat vocal fold paralysis has several advantages. For instance, it promotes vocal fold regeneration without injection medialization with foreign substances. Moreover, it uses an easily available commercialized formulation whose safety has already been established.[10] The bFGF used in this treatment is also known as FGF-2 or FGF-β and is one of the most common growth factors. For example, bFGF plays an important role in developmental processes such as nerve and limb development,[21] anterior–posterior patterning,[22] mesoderm induction, keratinocyte organization, angiogenesis in mature tissues and systems, and wound healing.[23] Moreover, bFGF stimulates intralaryngeal muscle proliferation. For example, Goto et al.[24] reported that in rats with recurrent laryngeal nerve paralysis, a single injection of bFGF augmented the regeneration and differentiation of atrophic thyroarytenoid muscles by enhancing the proliferation and differentiation of muscle satellite cells. In addition, Nagai et al.[25] conducted fascial transplantation experiments in rats with a severed recurrent nerve and demonstrated that

laryngeal framework surgery, MPT and MFR did not improve after the initial injection but improved after the framework surgery. To clarify the indications for a single bFGF injection, we compared the pre-injection voice laboratory measurements of the single-injection and additional treatment (injection or framework surgery) groups. Among the 10 items measured (including age and sex), there were significant differences in MPT, NHR, and tGRBAS values between the groups (Table 1). MPT was significantly greater in the single-injection group (mean, 7.1 s) than that in the additional treatment group (mean, 4.2 s). The mean NHR was significantly lower in the single-injection group (mean, 4.4) than in the additional treatment group (mean, 6.4). Furthermore, the tGRBAS score was significantly higher in the additional treatment group (mean, 6.1) than in the single-injection group (mean, 4.4) (Table 1). These results suggested that the more symptomatic patients (as measured by MPT, NHR, and tGRBAS values) often required additional treatment.

bFGF significantly reduced the glottic gap and increased the volume of residual fascia and fat in the paralyzed vocal folds. Tamura et al.[26] demonstrated that bFGF injection in the vocal fold helped maintain the adipose tissue in the paralyzed vocal cords of experimental beagle dogs. Computed tomography scans have also shown that UVFP patients treated with bFGF had a smaller decrease in the volume of injected fat tissue than patients treated with the conventional method.[27] These results suggest that bFGF has potentiating effects on the intralaryngeal muscles and effectively improves the symptoms caused by UVFP. In addition, bFGF might reverse the atrophy seen with chronic denervation as the glottal insufficiency, usually observed in atrophic vocal folds, was reduced in most cases in this study. Upon administering vocal fold injections of bFGF to patients with UVFP (who had not improved sufficiently after laryngeal framework surgery), we observed additional phonological improvements.[10] Another study reported that following vocal fold injection of bFGF, 19 patients with UVFP showed significant improvements in MPT, MFR, PR, and NHR values 6 months post-injection (compared with the pre-injection values).[14] These improvements were observed in both female (with small larynxes) and male patients (with larger larynxes).[14] Thus, previous results have demonstrated the short-term efficacy and safety of vocal fold bFGF injection therapy.[10,14] As mentioned earlier, the findings of our preliminary study indicated that bilateral bFGF injection led to more preferable outcomes than unilateral injection for UVFP. Although the reason for this is unclear, there are several possibilities. First, most patients with UVFP exhibited vocal fold atrophy on the contralateral side by poor vocalization or muscle tension dysphonia associated with UVFP. Second, the vibration of the vocal fold injected with bFGF differed from that of the unaffected vocal fold, and bilateral injection may have equalized the vibrations on both sides. Third, unilateral injection cannot achieve an adequate reduction of the glottic gap. The results showed that a single bFGF injection significantly improved the voice laboratory measurements—including MPT, MFR, PR, jitter, shimmer, tGRBAS, and VHI—at 6 months post-injection and that these improvements were maintained at 12 months post-injection. In stroboscopic findings, glottic insufficiency decreased, and the periodicity improved with an increase of the mucosal wave on the paralyzed side during phonation, and symmetry was observed between the healthy and paralyzed sides. However, in the six patients who received an additional bFGF injection, the changes in MPT and MFR values were temporary. Similarly, in the six patients who underwent additional framework surgery, bFGF injection did not improve the MPT and MFR values. However, significant improvements were observed after framework surgery in these patients. Therefore, framework surgery—and not an additional bFGF injection—should be used as an additional therapy for patients with ineffective bFGF injection.

In the present study, the pre-injection voice laboratory measurements (MPT, NHR, and tGRBAS values) were significantly different between the single-injection (effective) and additional treatment or laryngeal framework surgery (ineffective) groups. These results suggest that bFGF injection was less effective in patients with severe symptoms (in terms of voice efficiency and voice quality), and these symptoms were considered to be an indication for laryngeal framework surgery. Importantly, vocal fold bFGF injection did not interfere with the efficacy of framework surgery. The present study showed that except in some severe cases, bFGF injection was effective for the long-term improvement of voice disorders caused by UVFP. These results indicate that it is possible to provide a comprehensive treatment based on symptoms; for example, framework surgery may be used for the most severe cases, bFGF injection for severe to moderate cases, and voice rehabilitation for mild cases.

Although this study did not include a control group to estimate the spontaneous recovery cases, these cases could be excluded because the study participants did not improve for a 6-month period of voice rehabilitation. Furthermore, this study can be used as the pilot data for safety/efficacy and to create a future study with a control group to evaluate a short-acting injectable.

5 | CONCLUSIONS

In total, 42 patients who underwent vocal fold bFGF injections were reviewed. The bFGF injections were effective and safe in the long-term results for UVFP in the selected cases. Some patients with severe symptoms benefited from the additional framework surgery but not the additional bFGF injection.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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REFERENCES

1. Wang HW, Lu CC, Chao PZ, Lee FP. Causes of vocal fold paralysis. *Ear Nose Throat J.* 2020. doi:10.1177/0145561320965212
2. Kanazawa T, Watanabe Y, Hara M, et al. Arytenoid adduction combined with medialization laryngoplasty under general anesthesia using a laryngeal mask airway. *Am J Otolaryngol.* 2012;33(3):303-307.
3. Kashima K, Watanabe K, Sato T, Katori Y. Analysis of dysphagia and cough strength in patients with unilateral vocal fold paralysis. *Dysphagia.* 2021. doi:10.1007/s00455-021-10274-8
4. Walton C, Conway E, Blackshaw H, Carding P. Unilateral vocal fold paralysis: a systematic review of speech-language pathology management. *J Voice.* 2017;31(4):509.

5. Kanazawa T, Watanabe Y, Komazawa D, et al. Phonological outcome of laryngeal framework surgery by different anesthesia protocols: a single-surgeon experience. *Acta Otolaryngol*. 2014;134(2):193-200.

6. Kanazawa T, Komazawa D, Watanabe Y, Ichimura K. Revision laryngeal framework surgery performed by directly pulling the lateral cricoarytenoid muscle. *J Laryngol Otol*. 2014;128(10):935-938.

7. Pagano R, Morsomme D, Camby S, Lejeune L, Finck C. Long-term results of 18 fat injections in unilateral vocal fold paralysis. *J Voice*. 2017;31(4):505.

8. Choi N, Won S, Jin H, Kim HJ, Park W, Son YI. Additional injection laryngoplasty for patients with unilateral vocal fold paralysis. *Laryngoscope*. 2020;130(12):2863-2868.

9. Shiotani A, Okubo K, Saito K, et al. Injection laryngoplasty with calcium phosphate cement. *Otolaryngol Head Neck Surg*. 2009;140(6):816-821.

10. Kanazawa T, Komazawa D, Indo K, et al. Single injection of basic fibroblast growth factor to treat severe vocal fold lesions and vocal fold paralysis. *Laryngoscope*. 2015;125(10):E338-E344.

11. Langer R, Vacanti JP. Tissue engineering. *Science*. 1993;260(5110):920-926.

12. Atienza-Roca P, Cui X, Hooper GJ, Woodfield TBF, Lim KS. Growth factor delivery systems for tissue engineering and regenerative medicine. *Adv Exp Med Biol*. 2018;1078:245-269.

13. Okui A, Konomi U, Kanazawa T, et al. Therapeutic efficacy of basic fibroblast growth factor in patients with vocal fold atrophy. *Laryngoscope*. 2020;130(12):2847-2852.

14. Kanazawa T, Kurakami K, Kashima K, et al. Injection of basic fibroblast growth factor for unilateral vocal cord paralysis. *Acta Otolaryngol*. 2017;137(9):962-967.

15. Hirano S, Sugiyama Y, Kaneko M, Mukudai S, Fuse S, Hashimoto K. Intracordal injection of basic fibroblast growth factor in 100 cases of vocal fold atrophy and scar. *Laryngoscope*. 2021;131(9):2059-2064.

16. Ban MJ, Lee SC, Park JH, Park KN, Kim HK, Lee SW. Regenerative efficacy of fibroblast growth factor for the treatment of aged vocal fold: from animal model to clinical application. *Clin Otolaryngol*. 2021;46(1):131-137.

17. Hirano S, Bless DM, del Río AM, Connor NP, Ford CN. Therapeutic potential of growth factors for aging voice. *Laryngoscope*. 2004;114(12):2161-2167.

18. Suehiro A, Hirano S, Kishimoto Y, Rousseau B, Nakamura T, Ito J. Treatment of acute vocal fold scar with local injection of basic fibroblast growth factor: a canine study. *Acta Otolaryngol*. 2010;130(7):844-850.

19. Hirano S, Nagai H, Tateya I, Tateya T, Ford CN, Bless DM. Regeneration of aged vocal folds with basic fibroblast growth factor in a rat model: a preliminary report. *Ann Otol Rhinol Laryngol*. 2005;114(4):304-308.

20. Kanazawa T, Nokubi M, Takeoda K, Kodama K, Usubuchi H, Iino Y. Atypical carcinoid of the larynx and expressions of proteins associated with molecular targeted therapy. *Auris Nasus Larynx*. 2011;38(1):123-126.

21. Böttcher RT, Niehrs C. Fibroblast growth factor signaling during early vertebrate development. *Endocr Rev*. 2005;26(1):63-77.

22. Koga C, Adati N, Nakata K, et al. Characterization of a novel member of the FGF family, XFGF-20, in *Xenopus laevis*. *Biochem Biophys Res Commun*. 1999;261(3):756-765.

23. Matsumoto S, Tanaka R, Okada K, et al. The effect of control-released basic fibroblast growth factor in wound healing: histological analyses and clinical application. *Plast Reconstr Surg Glob Open*. 2013;1(6):e44.

24. Goto T, Ueha R, Sato T, Fujimaki Y, Nito T, Yamasoba T. Single, high-dose local injection of bFGF improves thyroarytenoid muscle atrophy after paralysis. *Laryngoscope*. 2020;130(1):159-165.

25. Nagai H, Nishiyama K, Seino Y, Tabata Y, Okamoto M. Evaluation of autologous fascia implantation with controlled release of fibroblast growth factor for recurrent laryngeal nerve paralysis due to long-term denervation. *Ann Otol Rhinol Laryngol*. 2016;125(6):508-515.

26. Tamura E, Fukuda H, Tabata Y. Adipose tissue formation in response to basic fibroblast growth factor. *Acta Otolaryngol*. 2007;127(12):1327-1331.

27. Tamura E, Tabata Y, Yamada C, Okada S, Iida M. Autologous fat augmentation of the vocal fold with basic fibroblast growth factor: computed tomographic assessment of fat tissue survival after augmentation. *Acta Otolaryngol*. 2015;135(11):1163-1167.

SUPPORTING INFORMATION

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