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META-ANALYSIS

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The use of basic fibroblast growth factor to improve vocal function: A systematic review and meta-analysis

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Abstract

Objectives: This systematic review and meta-analysis examines if intralaryngeal injection of basic fibroblast growth factor 2 (FGF2) can improve voice outcomes in those with vocal disability.

Design: A Systematic review of original human studies reporting voice outcomes following intra-laryngeal injection of basic fibroblast growth factor 2 in those with vocal dysfunction. Databases searched were Medline (1946–July 2022), Embase (1947–July 2022), Cochrane database and Google Scholar.

Setting: Secondary or tertiary care centres that undertook the management of voice pathology Hospital.

Participants: Inclusion criteria were original human studies reporting voice outcome measurements following intralaryngeal injection of FGF2 to treat vocal fold atrophy, vocal fold scarring, vocal fold sulcus or vocal fold palsy. Articles not written in English, studies that did not include human subjects and studies where voice outcome measures were not recorded before and after FGF2 injection were excluded from the review.

Main Outcome Measures: The primary outcome measure was maximum phonation time. Secondary outcome measures included acoustic analysis, glottic closure, mucosal wave formation, voice handicap index and GRBAS scale.

Results: Fourteen articles were included out of a search of 1023 and one article was included from scanning reference lists. All studies had a single arm design without control groups. Conditions treated were vocal fold atrophy ($n = 186$), vocal cord paralysis ($n = 74$), vocal fold fibrosis ($n = 74$) and vocal fold sulcus ($n = 56$). A meta-analysis of six articles reporting on the use of FGF2 in patients with vocal fold atrophy showed a significant increase of mean maximum phonation time of 5.2 s (95% CI: 3.4–7.0) at 3–6 months following injection. A significant improvement in maximum phonation time, voice handicap index and glottic closure was found following injection in most studies assessed. No major adverse events were reported following injection.

Conclusions: To date, intralaryngeal injection of basic FGF2 appears to be safe and it may be able to improve voice outcomes in those with vocal dysfunction, especially vocal fold atrophy. Randomised controlled trials are needed to further evaluate efficacy and support the wider use of this therapy.

KEYWORDS
FGF2, fibroblast growth factor, vocal cord, voice

1 | INTRODUCTION

Relative differences in the viscoelasticity of the vocal fold lamina propria are essential for coordinated vocal fold vibration and optimal voice quality. Loss of viscoelastic lamina propria, especially when occurring in the superficial layer, are a common cause of chronic vocal disability. Currently, there is no established treatment to restore viscoelastic tissue within the vocal fold. Experimental therapies using biomaterials, growth factors and/or mesenchymal stem cells have been tested in animal models with some reported success.[1–3] However, few of these have reached clinical trials and significant challenges remain in terms of scalability and manufacturing cost. A notable exception is the use of basic fibroblast growth factor (FGF2), which has been trialled in human subjects since 2008.[4] FGF2 is a growth factor that stimulates the migration and proliferation of vocal fold fibroblasts and has been shown to stimulate the secretion of proteins important for viscoelasticity and suppress the deposition of fibrous protein.[5] FGF2 is relatively inexpensive to manufacture and can be injected into the vocal fold using routine in-office procedures via a trans-oral or transcutaneous route. This provides a significant advantage over more complex biotherapies and greatly increases its potential to be adopted as a new globalised clinical therapy for chronic vocal disability.

Key points

- Mean maximum phonation time increased significantly after injection of FGF2 in those with vocal fold atrophy in the meta-analysis.
- Acoustic analysis outcomes were more variable but may represent difficulties with assessing global voice improvement with the methods used.
- Significant improvements in maximum phonation time and voice handicap index were achieved with a single injection of FGF2.
- To date, injection of FGF2 appears to be safe with no major adverse events recorded in 390 cases examined.
- Controlled trials with the use of a placebo arm are needed to confirm efficacy.

1.1 | Objectives

The objectives of this article were to establish whether intralaryngeal injection of FGF2 improve voice outcomes in those with an existing vocal disability. The review will also examine improvements in mucosal wave and glottic closure following injection and examine the safety profile of this therapy.

2 | METHODS

A systematic review of literature was performed by one reviewer with specific reference to the use of basic FGF2 to restore vocal function following the PRISMA reporting guideline (Figure 1).

2.1 | Ethical considerations

This review did not require ethical committee approval.

2.2 | Eligibility criteria

All original human studies reporting voice outcomes following injection of FGF2 were included. The inclusion criteria were: Studies written in English, studies examining vocal disability caused by vocal fold atrophy, vocal fold scarring, vocal fold sulcus or vocal fold immobility. Objective outcome measurements were acoustic and aerodynamic analysis of voice and measurements of glottic gap. Subjective outcomes were the voice handicap index (VHI) questionnaire, the perceptual voice grading system, GRBAS and assessments of vocal fold mucosal wave during phonation. Exclusion criteria were: Articles not written in English, animal studies and articles lacking outcome measures before and after injection of FGF2.

2.3 | Databases and search strategy

Databases searched were Medline (1946–20 July 2022) and Embase (1947–20 July 2022). Cochrane database and Google Scholar were also reviewed. The search strategy used the terms 'fibroblast growth factor' or 'basic fibroblast growth factor' or 'fibroblast growth factor two' or 'FGF2' or 'FGF' and 'vocal cord' or 'vocal fold' or 'larynx' or 'Reinke's space' or 'sulcus vocalis' or 'presbylaryngis' or 'paresis' or 'palsy' or 'voice' (Appendix 1). No filters or restrictions were applied. The primary outcome measure for this study was maximum phonation time (MPT). Secondary outcome measures were acoustic analysis, patient-reported VHI scores, the perceptual voice grading system GRBAS and improvements in mucosal wave and glottic closure.

2.4 | Data selection and collection

One reviewer identified relevant articles. Reference lists were scanned for further relevant articles. Identified international experts in

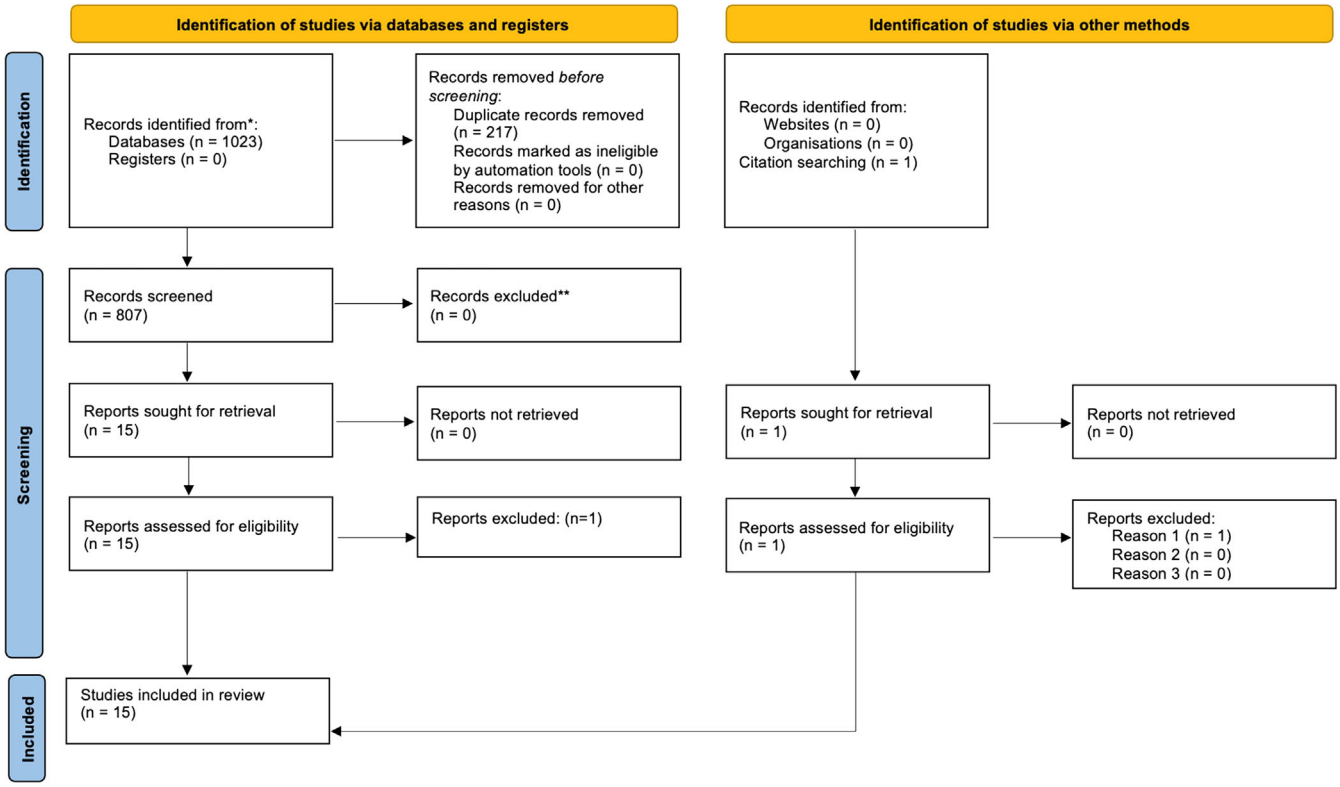

FIGURE 1 Flow diagram presenting process of study selection. *Source*: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

laryngology and tissue-engineering sciences were approached for their views on the most important published and unpublished studies in this field. Duplicates were removed from the initial search. Records that met the inclusion criteria were screened based on title abstract. Full-text articles were reviewed for eligibility and those not relevant were excluded.

2.5 | Study risk of bias assessment

The risk of bias was determined using the ROBINS-I tool for determining risk of bias in non-randomised intervention studies.[6] A funnel plot and Egger's test,[7] were used to investigate the possibility of publication bias.

2.6 | Synthesis methods

The mean and standard deviation of MPT were recorded before injection and 3–6 months after injection. The values were recorded or calculated from data provided in the reports or extrapolated from the error bars on graphs. Information (i.e., standard deviation) was not available on the differences between values. Given the heterogeneity in the underlying cause of vocal disability, only MPT data derived from vocal fold atrophy were pooled using a random effects meta-analysis (with τ^2 estimated using REML). Forest plots were used to summarise the results and heterogeneity was quantified using the I^2 statistic.

3 | RESULTS

3.1 | Study selection and characteristics

A total of 1023 articles were found matching the search criteria. Records after duplicates removed were 807. Fifteen of which fulfilled the entry criteria. One article was excluded as it did not report on the assessment of voice outcomes following injection of FGF2. One article was found from scanning reference lists. Fifteen studies were taken forward for analysis (Figure 1).[4,8–21]

The total number of study participants across all 15 reports was 390 (median: 17, IQR: 11–31). Conditions treated were vocal fold atrophy ($n = 186$), vocal cord paralysis ($n = 74$), vocal fold scar ($n = 74$) and vocal fold sulcus ($n = 56$) (Table 1). Data collection was prospective ($n = 13$) and retrospective ($n = 2$) and involved a single treatment arm in all cases. Follow-up ranged from 3 months post-injection to 36 months. A transoral method of injection was used in six studies, a transcutaneous method of injection via the cricothyroid or thyrohyoid membrane was used in eight studies and in one study, injection was administered via the side port of a flexible nasolaryngoscope.

3.2 | Assessment of bias

Bias was assessed using the ROBINS-I tool (Appendix 2). Bias in selection of participants into the study and in classification of interventions

TABLE 1 Fifteen studies were included for analysis.

Study	Date	1st author	Pathology	Injection method	Number of patients	Follow-up (months)
1	Apr 2022	Yamauchi	P	Trans-nasal	42	12
2	Oct 2021	Sueyoshi	A, Sc, Su	Perc	6	24
3	Jan 2021	Miura	A, P, Su	Trans-oral	19	36
4	Oct 2020	Hirano	A, Sc, Su	Trans-oral	100	48
5	Jun 2020	Ban	A	Perc	38	12
6	Jan 2020	Okui	A	Perc	53	6
7	Feb 2019	Kanazawa	Su	Perc	12	4
8	Dec 2017	Ban	Sc	Perc	17	12
9	Feb 2017	Kanazawa	P	Perc	19	12
10	Sep 2015	Suzuki	A, P, Su	Perc	17	12
11	Aug 2016	Ohno	A	Trans-oral	6	6
12	Mar 2015	Kanazawa	A, P, Sc, Su	Perc	35	3
13	Feb 2013	Hirano	Sc, Su	Trans-oral	15	6–24
14	Aug 2011	Hirano	A	Trans-oral	10	12
15	Jun 2008	Hirano	A	Trans-oral	1	3

Note: Studies examined patients with vocal cord palsy (P), vocal fold atrophy (A), vocal fold scarring (Sc) or vocal fold sulcus (Su). Injections were delivered via a trans-oral route using a curved injection needle, a trans-nasal route using a flexible endoscope with side channel or percutaneously (perc) via the thyrohyoid or cricothyroid membrane.

was graded as low across all studies. Bias due to deviations from intended interventions was graded as moderate in six studies as a varying number of injections were given depending on how the patient responded to the first injection. Bias in missing data was graded as moderate in one study, low in nine studies and in five studies, the completeness of follow-up data could not be assessed. Bias in measurement of outcomes was graded as moderate in four studies due to the absence of measures to control for inter-rater variability in subjective voice outcome measures such as the GRBAS scale. Bias in selection of reported results was low in 14 studies and moderate in one, where an assessment of glottic closure was included in the methods but not reported in the results. As all studies involved a single treatment arm, bias due to confounding factors were not assessed.

3.3 | Voice outcomes following FGF2 injection

A range of outcome measures were used (Table 2). MPT was assessed in 14 studies and showed a significant improvement in 12 studies up to 6 months post-injection and six out of the seven studies that reporting at 12 months or greater post-injection (Figure 1). Meta-analysis showed a significant increase in mean MPT of 5.2 s (95% CI: 3.4–7.0) at 3–6 months following injection (Figure 2). The I^2 statistic was 0%, suggesting no heterogeneity between studies. There was no evidence of publication bias from Egger's test ($p = .79$) (Funnel plot in Supporting Information S1).

The VHI was used as a patient-reported voice outcome measure following injection in 6 out of 14 studies and the shorter, voice handicap index 10 (VHI-10), was used in 5 out of 14 studies. The mean VHI score was 54.6 pre-injection, 29.7 at 4 months post-injection and 26.7 at 6 months post-injection. The mean VHI-10 score was 21 pre-injection, 10.5 at 6 months post-injection and 10 at 12 months post-injection. Improvements in VHI and VHI-10 were all statistically significant in all 11 studies.

The perceptual voice grading system, GRBAS, was used in 7 out of 15 cases in the short-term and 5 out of 7 cases in the long-term. Mean GRBAS was 5.7 pre-injection, 2.5 within 6 months of injection and 1.8 a year or more after injection. A significantly reduced mean GRBAS score was recorded for all studies. To control inter-rater reliability, 2–3 raters were used in four of the studies.[10,11,17,20] Of these four studies, two reported using independent assessors.[11,20] In three studies, no method to control inter-rater reliability was described.[8,12,15]

Mucosal wave and glottic closure were assessed using either an independent four-point scale (Reports 5 and 8) or motion analysis software (Reports 3, 10 and 11). In all cases, a significant improvement in glottic closure and mucosal wave characteristics were reported. Acoustic analysis of voice showed more variable improvement in both short-term and long-term timepoints following injection (Table 2).

3.4 | Sub-group analysis

Out of the six studies that investigated different vocal fold pathologies, two provided a sub-group analysis. Hirano et al.[11] grouped sulcus and scar patients and graded them as mild, moderate or severe. VHI-10 scores improved more in the mild and moderate cases following FGF2 injection compared to severe cases. Improvements in VHI-10 were also significantly greater amongst patients with vocal fold

TABLE 2 The outcome measures used before and after injection of FGF2.

			0–6 months													
			Acoustic analysis								Aerodynamic analysis					
Report	Dose (mcg)	Injection frequency	Jitter	Shimmer	NHR	VRP	MDVP	PR	SFF	SPL	MPT	MFR	Mucosal wave	Glottic closure	VHI	GRBAS
1	.25	1	*	*	×			*	×		*	*			*	*
2	10	4	*	×	×	×	×	×	*	×	*	×			*	
3	2–4	1	*	×							*			*		*
4	10	4(2)									*				*	*
5	10	1	*	×	×	*					*		*	*	*	*
6	50	1	*	*	×			*			*	×			*	
7	50	1 (2–3)	×	×	*			*	*	×	*	×			*	
8	20–30	1	×	×	×				*		*		*	*	*	*
9	50	1	×	×	×			*	×		*	*			*	
10	2–4	1	×	×	×						*			*		*
11	10	1	×	×							×		*	*	*	
12	50	1	*	×	×			*	*		*	*			*	
13	10	4(2)									×				*	*
14	10	4(2)	×	*	*						*	*				
15	10	1														
			≥12 months													
			Acoustic analysis								Aerodynamic analysis					
Report	Dose (mcg)	Injection frequency	Jitter	Shimmer	NHR	VRP	MDVP	PR	SFF	SPL	MPT	MFR	Mucosal wave	Glottic closure	VHI	GRBAS
1	.25	1	*	*	×			*	×		*	*			*	*
2	10	4	*						*		×	×			*	
3	2–4	1	×	×							*			*		*
5	10	1	*	*	*	×					*		*	*	*	*
8	20–30	1	×	×	×				*		*		*	*	*	*
10	2–4	1	×	×	×						*			*		*
14	10	4(2)	*	*	*						*	×				

Note: The outcome measures used before and after injection of FGF2 in each report are presented along with the dose of FGF2 administered and the number of injections per patient (brackets represent a repeated cycle of injections). *Represents a significant improvement and × represents no significant improvement in the outcome measure following injection of FGF2. Blank boxes indicate that the outcome measure was not used. Boxed are shaded determining on the indication for treatments was vocal cord palsy (green), vocal fold atrophy (blue), sulcus or scar (yellow) or a mix of pathologies (grey).

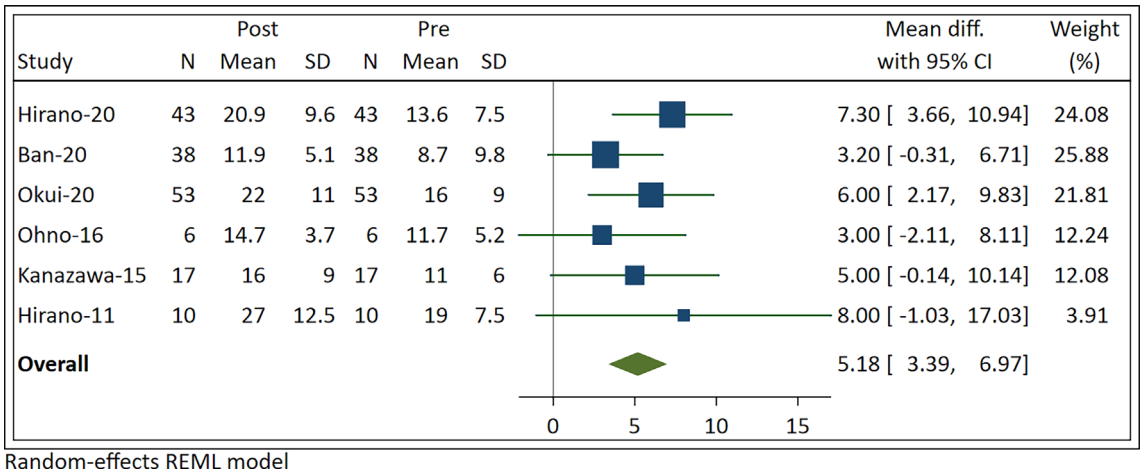

FIGURE 2 Meta-analysis showed a significant increase in mean MPT of 5.2 s at 3–6 months following injection ($p < .0001$, CI: 3.4–7.0) in cases of vocal fold atrophy. The I2 statistic was 0%, suggesting no heterogeneity between studies. There was no evidence of publication bias from Egger's test ($p = .79$) on the meta-analysis of maximum phonation time (Funnel plot in Supporting Information S1).

atrophy compared to patients with scar or sulcus. Kanazawa et al.[19] ranked improvement in MPT and found the greatest improvement in vocal fold atrophy followed by paralysis and then scar and sulcus. The impact of age was also explored and improvements in MPT following injection were found to have an inverse relationship to age. However, Okui et al.[13] found no effect of age on MPT or VHI when comparing those over 70 years of age and those under 70 years with vocal fold atrophy.

3.5 | Injection method and adverse events

All studies used recombinant human FGF2 (Fiblast, Kaken Pharmaceutical, Tokyo, Japan). Four reports used a dose of 10 mcg given four times at 1-week intervals and repeated at 3 months if no improvement was found (Table 1). Three reports used a single dose of 10 mcg. Four reports used a single dose of 50 mcg, which in one report, was repeated up to three times if no improvement was recorded after 4 months. All other studies used a single injection ranging between .25, 2–4 and 20–30 mcg. Given the variability in study methodology, data synthesis was not possible to calculate dose effect. As shown in Table 1, similar outcomes were observed irrespective of dose and timing.

FGF2 was injected into vocalis muscle in one study of patients with vocal fold paralysis. The remaining reports injected FGF2 into superficial lamina propria of the vocal fold. In cases of atrophy, injection was bilateral and in cases of scar and sulcus injections were into the affected vocal fold. In cases of vocal fold paralysis, injections were into the affected side in Study 3 and 12 and into both vocal folds in Studies 1 and 10.

Ten studies commented on the incidence of adverse effects following injection.[8,11,12,14–16,18–21] Out of these 10, no major adverse events were reported. Transient hyperemia of the vocal fold with associated transient vocal hoarseness was consistently reported. In Hirano et al.,[11] where 100 patients were followed up, hyperemia occurred in 72% and was graded as mild in 66% and severe in 6%. In all cases, the hyperemia had resolved by 2 months post-injection.

4 | DISCUSSION

Out of 390 cases examined, no major adverse events were reported. This indicates intralaryngeal injection of FGF2, to date, is safe although evaluation of further cases is needed to identify rarer events that may arise.

Significant improvements in MPT and VHI across most studies in both the short and long-term suggest intracordal injection of FGF2 may be efficacious in improving voice production and the experience of vocal handicap in those with a chronic disability. Future investigations should provide more comprehensive outcome data and, where investigating different pathologies, should include a sub-group analysis to enable data synthesis and meta-analysis. Improved glottic closure and mucosal wave characteristics following injection indicate restoration of a normal phonatory vibration pattern. Significant improvements in these parameters were recorded following injection but the use of multiple independent assessors was only described in one report. Likewise, with the reporting of GRBAS scales, only four of the seven studies deployed methods to limit inter-rater variability and only two reported these using independent assessors. Multiple independent assessors are important to limit bias given the subjectivity of these outcome measurements and should be included in future studies.

Outcomes derived from acoustic analysis were less consistent in demonstrating significant improvement. Limitations associated with the use of singular acoustic measures, particularly those based on cycle-to-cycle perturbations, in capturing global voice quality improvement following treatment are well known; they require a

voice source that is periodic and are usually only applicable for sustained vowels of stable pitch and loudness. More robust measures, such as those based on cepstral analysis, were not reported in any of the included studies. The use of a multivariate acoustic measurement, where multiple acoustic parameters and cepstral parameters are assessed and synthesised into a single measure of dysphonia, have been shown to significantly correlate with auditory-perceptual assessments of voice quality and would thus provide a more sensitive assessment of overall voice quality than any one measure in isolation.[22,23] One such measure, the acoustic voice quality index (AVQI) is validated in 13 languages and combines acoustic measurements from both sustained vowels and connected speech, reflecting a more ecologically valid assessment of a subject's voice production. It has been shown to provide a robust objective measurement of voice quality in meta-analysis and would be a useful tool in future studies.[24]

Significant improvements in voice outcomes with a single injection of FGF2 indicate multiple injections during the first treatment cycle may not be necessary. Several studies used additional injections if no improvement in voice outcomes were detected at follow-up and recorded subsequent improvement. Given FGF2 has a half-life of approximately 8 h,[25] the long-term effect of a single injection is believed to be mediated through persisting changes in intracellular gene expression that favour extracellular matrix regeneration. Experimental studies demonstrating this using modern genomic techniques, such as RNA sequencing, would be useful in establishing the mechanism behind this observation. The same experiments could also be used to understand the dose effect given the wide variation in dosing regimens in the reported studies.

The single-arm design of the studies included in this review is a clear limitation. Given the safety profile of in-office intracordal injection, the use of a placebo arm could be justified as part of a randomised controlled trial. Alternatively, a superiority trial, comparing FGF2 to existing treatments, or a dose–response trial could be considered. This would provide evidence on the efficacy of FGF2 to improve voice outcomes and could lead to a more widespread adoption of this therapy. Similar study designs have been used to demonstrate efficacy with the application of FGF2 in tympanic membrane healing following perforation and periodontal regeneration in intrabony defects.[26,27]

5 | CONCLUSION

To date, the injection of intralaryngeal FGF2 to treat vocal dysfunction appears safe and there is evidence supporting efficacy in improving voice outcomes. Future studies should aim to include a control group and should deploy multivariate acoustic measurements to achieve a more global assessment of voice quality.

FUNDING INFORMATION

No external funding or support was provided for this review.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX 1: SEARCH STRATEGIES

Database: Medline (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) 1946 to present.

1. 'fibroblast growth factor' or 'basic fibroblast growth factor' or 'fibroblast growth factor 2' or 'FGF2' or 'FGF'.

2. 'vocal cord' or 'vocal fold' or 'larynx' or 'Reinke's space' or 'sulcus vocalis' or 'presbylaryngis' or 'paresis' or 'palsy' or 'voice'.

3. 1 and 2.

APPENDIX 2: ROBIS-I TOOL

Date of publication	Lead author	Selection of participants	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of the reported results
Apr 2022	Yamauchi	Low	Low	Moderate	Moderate	Low	Low
Oct 2021	Sueyoshi	Low	Low	Moderate	Low	Moderate	Low
Jan 2021	Miura	Low	Low	Moderate	Low	Low	Low
Oct 2020	Hirano	Low	Low	Moderate	Low	Low	Low
Jun 2020	Ban	Low	Low	Moderate	Low	Moderate	Low
Jan 2020	Okui	Low	Low	Low	NI	Low	Low
Feb 2019	Kanazawa	Low	Low	Moderate	Low	Low	Low
Dec 2017	Ban	Low	Low	Low	Low	Moderate	Low
Feb 2017	Kanazawa	Low	Low	Low	Low	Low	Low
Sep 2015	Suzuki	Low	Low	Moderate	NI	Low	Low
Aug 2016	Ohno	Low	Low	Low	NI	Low	Low
Mar 2015	Kanazawa	Low	Low	Low	NI	Low	Low
Feb 2013	Hirano	Low	Low	Low	Low	Low	Low
Aug 2011	Hirano	Low	Low	Moderate	NI	Moderate	Moderate