The Egyptian Journal of Otolaryngology

ORIGINAL ARTICLE Open Access

Respiratory and voice outcomes of office-based injection laryngoplasty in patients with unilateral vocal fold paralysis

Asser Elsaeed[1], Omayma Afsah[1*], Waleed Moneir[2], Tamer Elhadidy[3] and Tamer Abou-Elsaad[1]

Abstract

Background: Injection laryngoplasty is a surgical procedure used in management of glottal insufficiency. The objective of this study was to assess respiratory and voice outcomes of office-based injection laryngoplasty in patients with unilateral vocal fold paralysis (UVFP). Ten patients underwent office-based injection via transcutaneous approach using Radiesse or hyaluronic acid. Auditory perceptual assessment (APA), voice handicap index (VHI), size of the glottic gap, acoustic parameters (jitter, shimmer, and harmonic to noise ratio), maximum phonation time (MPT), stroboscopic evaluation, pulmonary function tests (PFTs), and videofluoroscopic evaluation of swallowing were done pre-injection, 1 week and 3 months post-injection.

Results: Subjective and objective voice outcomes, in addition to laryngostroboscopic parameters improved after injection. Non-significant difference was found between pre- and post-injection results of the PFTs.

Conclusions: Office-based injection laryngoplasty is a safe and effective method for treating UVFP. Patients with glottic gap (< 1–3 mm) are perfect candidates for such procedure. Injection laryngoplasty improves patients' voice quality and does not impair respiration.

Keywords: Vocal fold immobility, Office-based, Injection laryngoplasty, Radiesse

Background

Vocal fold paralysis (VFP) refers to vocal fold (VF) immobility caused by neurologic injury [1]. The etiology of unilateral vocal fold paralysis (UVFP) includes malfunction of the nuclei of the brainstem, the 10th cranial nerve (vagus), or the recurrent laryngeal nerve that supplies the corresponding side of the larynx. The commonest cause of UVFP is likely iatrogenic. Many neck and thoracic surgeries might be complicated by UVFP. Another common etiology of UVFP is non-laryngeal malignancies (e.g., bronchogenic carcinoma) [2].

The abducted VF in UVFP will affect the quality of voice resulting in breathiness, diplophonia, reduced loudness, decreased phonation time, and a restricted pitch range [3]. Shortness of breath and dysphagia were also reported by patients with UVFP [2, 4]. In their survey on 63 patients with UVFP, Brunner et al. [5] mentioned that 60% of surveyed patients complained of swallowing problems following the onset of paralysis and 75% reported a subjective breathing impairment, not just phonatory dyspnea but during every day physical activity as well.

Spirometry is a screening physiological test of general respiratory health [6]. The most commonly used measures include the forced vital capacity (FVC), the forced expiratory volume in one second (FEV_1), and the ratio of the two (FEV_1/FVC). Interpretations of spirometry results require comparison between an individual's measured value and the predicted value [7]. If the FVC and the FEV_1 are within 80% of the predicted value, the results are considered normal. The ratio FEV_1/FVC is

* Correspondence: omafsah@yahoo.com
[1]Phoniatric Unit, ORL Department, Faculty of Medicine, Mansoura University, Mansoura 35516, Egypt
Full list of author information is available at the end of the article

between 70 and 80% in normal adults; a value less than 70% suggests airflow limitation [8].

Management plan for UVFP offers immediate treatment to patients with permanent disability, while sparing those who are likely to recover from unwanted surgery. As a secondary goal, temporary relief from dysphonia and swallowing difficulties would be offered to this second group of patients while waiting for improvement [4].

Different therapy options were proposed for patients with UVFP based on the size of the glottic gap. Voice therapy is most suitable for patients with glottic gap less than 1 mm [9]. Injection augmentation is reserved for those with small (1 mm) or medium-sized (2–3 mm) glottic gap [4]. Patients with glottic gap more than 3 mm are suited for laryngeal framework surgery whether medialization laryngoplasty or arytenoid adduction [2]. Other therapy options include laryngeal reinnervation [4], laryngeal pacing [10], and regenerative stem cells [11].

In-office vocal fold injection encompasses percutaneous (trans-cricothryoid membrane, trans-thyroid cartilage, and trans-thyrohyoid membrane), per-oral, and trans-nasal endoscopic approaches [12]. Observing VF closure and voice outcome during the procedure are distinct advantages of office based vocal fold injection under local anesthesia, thus avoiding limitations of difficult exposure, and avoiding general anesthesia with its drawbacks [13].

Materials used for augmentation are categorized into temporary and long-lasting (sometimes permanent) materials. Temporary injection materials include bovine gelatin (Gelfoam™, Surgifoam™), collagen-based products (Zyplast™, Cosmoplast™/Cosmoderm™, Cymetra™), carboxymethylcellulose (Radiesse Voice Gel™), and hyaluronic acid gel (Restylane™, Hyalaform™). Long-lasting injection materials include autologous fat, calcium hydroxylapatite (CaHA) (Radiesse™), and Teflon [2].

Radiesse (CaHA) is one of the long-acting materials that have FDA approval and it is naturally found in the human body. It is composed of microspheres of CaHA (25–45 μm in diameter) suspended in a temporary gel carrier (water, glycerin, carboxymethylcellulose), which permits injecting the material easily via a small needle as the 25 gauge one [2]. In contrast to Radiesse which lasts for 18.6 months [14], the effect of hyaluronic acid lasts for 4 to 6 months, and some reported that it may last up to 9 months [2].

The majority of studies evaluating the outcomes of injection laryngoplasty in patients with UVFP focused on voice evaluation by subjective voice analysis using the Voice Handicap Index (VHI) (e.g., [14–16]), and most of them applied a retrospective study design. Only a minority of studies investigated the effect of injection laryngoplasty on respiratory functions in UVFP patients using either subjective or objective means. These studies yielded conflicting results.

The objective of this study was to evaluate the short-term respiratory and voice outcomes of office-based injection laryngoplasty in patients with unilateral vocal fold paralysis in order to determine its effectiveness as a promising therapy option for those patients and also to detect effect of injection over different time intervals.

Methods

This study was a prospective interventional study that was conducted on a sample of 10 patients with UVFP in the age range 20–60 (mean 41.9 ± 13.1) years who attended the outpatient clinic of Phoniatrics from November 2015 to November 2017. The referral complaint of all patients was dysphonia. Patients were enrolled in the study if they had a paralytic glottic gap 1–3 mm at maximum width and at least 2 months after the onset of UVFP. The date of onset of UVFP was defined as the date of surgery for those patients in whom the etiology was surgical intervention or by the patient's report of the onset of dysphonia in patients without history of surgery. Patients with laryngeal carcinoma and those with history of laryngeal irradiation were excluded from the study.

Patients were evaluated using the following protocol of assessment before injection, 1 week after, and 3 months after injection.

Subjective voice evaluation

Auditory perceptual assessments (APA) of voice were conducted using modified GRBAS (Grade, Roughness, Breathiness, Aesthenia, Strain) scale [17] with 4 grades from 0 (normal) to 3 (severe dysphonia) for determining grade and character of dysphonia. APA was recorded using dynamic microphone (Radioshack 3300660) and laptop (HP 620).

Prior to injection and at each follow-up visit, patients were asked to complete the Voice Handicap Index (VHI) "Arabic version" [18], which is patient-based survey to detect functional, physical, and emotional features of the handicap caused by voice impairment. Subscale scores range from 0 to 40 and the total scores range from 0 to 120. The higher the score, the greater the degree of handicap is detected.

Objective voice evaluation

Laryngoscopic examination was done using 70° rigid laryngoscope (Karl Storz) to determine side of paralysis and size of the glottic gap. Within (1–3 mm) glottic gap, we classified the gaps according to area of contact between both VFs into 5 grades as suggested by Lu et al. [19] as follows: 0 = complete closure, l = minimal

posterior gap involving the cartilaginous portion of the VFs only, 2 = posterior gap involving < 50% of the membranous VFs, 3 = posterior gap involving > 50% of the membranous portion but < 100% of the length of the true VFs, 4 = no contact between the true VFs.

For acoustic analysis, each patient sat in a quiet room with a dynamic microphone (Radioshack 3300660) 3 cm from his mouth and laptop (HP 620) was used to record a prolonged /a/ sound. Those voice samples were analyzed using PRAAT 64-bit edition [20] to obtain jitter, shimmer, and harmonic to noise (H/N) ratio.

For aerodynamic analysis, maximum phonation time (MPT) was measured in seconds using a stop watch during production of prolonged /a/ sound at comfortable pitch and loudness.

Laryngostroboscopic evaluation

It was done using 70° rigid laryngoscope (Karl Storz) that was interfaced with a stroboscopy unit (STORZ pulsar II 40160120) and a camera (LEMKE MC 204) for observing glottic wave, amplitude of vocal fold vibration, symmetry of the wave, phase closure of the glottis, and ventricular folds. For practical purposes, all parameters were graded on 3-point scale from 1 to 3 as follows: mucosal wave (1 = normal. 2 = decreased, 3 = absent), amplitude of vocal fold vibration (1 = normal, 2 = decreased, 3 = no visible movement), symmetry of the wave (1 = symmetry in both time and amplitude, 2 = asymmetry in either time or amplitude, 3 = asymmetry in both time and amplitude), phase closure of the glottis (1 = normal, 2 = closed phase predominates, 3 = open phase predominates), and ventricular folds (1 = normal, 2 = hypertrophied but not sharing in phonation, 3 = hypertrophied and sharing in phonation).

Pulmonary function tests

Pulmonary function tests were conducted at chest department, Mansoura university hospitals. Forced vital capacity (FVC), forced expiratory volume (FEV) in 1 s, peak expiratory flow (PEF), FEV1/FVC, and FEV/PEF were calculated using a spirometer "Smart PFT CO" device manufactured by medical equipment Europe-Hammelburg-Germany.

Videofluoroscopic swallowing study (VFSS)

Videofluroscopic swallowing study was done using Philips (Flexa Vision Shimadzu) device to detect aspiration during the swallow. Thin and thick liquids (both 3 ml and 5 ml volumes), semisolid, and solid consistencies were examined.

Injection procedure

Percutaneous injection of the paralyzed vocal fold was done under local anesthesia via the transcutaneous approach through the cricothyroid membrane, at the otorhinolaryngology department in the recovery room next to the operating theater. Injecting materials were supplied as commercially available preparation and came ready to use in self-contained syringes. The materials used in the study were hyaluronic acid (Perfectha deep) and calcium hydroxylapatite (Radiesse). Perfectha deep (20 mg/ml of hyaluronic acid) was used in patients in whom the onset of paralysis was less than 6 months while Radiesse (consisting of 30% synthetic CaHA microspheres suspended in a 70% aqueous carboxymethylcellulose gel carrier) was used in patients in whom the onset of paralysis was more than 6 months. Global anesthesia to the laryngeal and oropharyngeal mucous membranes was done with xylocaine pump spray 4% (about 2 ml) that were sprayed deeply into the patient's mouth. The patient was then asked to swallow and gurgle to ensure the spread of anesthesia in the larynx. Additional amount was given during the procedure when needed but never exceeding the safe dose (5 mg/kg). In irritable patients, 1 cm of lidocaine hydrochloride 2% was injected into the subglottic space through the cricothyroid membrane to ensure anesthetizing the whole subglottic space and the under surface of the VFs. A disposable 25 gauge needle was used for introducing the injectate into the affected VF via cricothyroid membrane under guidance of fiberoptic flexible laryngoscope (Henke-Sass-Wolf) interfaced with a camera (LEMKE MC 204). When the needle reached the VF, it was positioned correctly by moving its tip back and forth. Injections were administered either into or lateral to the vocalis muscle. The needle was introduced as lateral as possible and deep to avoid injection into the Reinke's space. Amount of the injectate used ranged from 0.75 to 1.5 ml. Patients were instructed not to phonate in the first 24 h after injection in order to avoid extrusion of material from injection site.

Statistical analysis

The statistical analysis of data was done by SPSS program version 21. The normality of data was first tested with Shapiro-Wilk test. Mean and standard deviation were calculated for parametric quantitative data. Median, minimum and maximum were calculated for non-parametric quantitative data. Qualitative data was described using frequency and proportion. Analysis of data between two paired groups (pre and post) was done using Wilcoxon test for quantitative data and chi-square test for qualitative data. P values less than 0.05 were considered statistically significant.

Results

Descriptive statistics

This study was conducted on 10 patients (4 males, 6 females) in the age range 20–60 (mean 41.9 ± 13.1) years with UVFP. The etiology of VFP was thyroid surgery in

five patients (50%), thoracic surgery in one patient (10%), and idiopathic in four patients (40%). The right VF was paralyzed in five patients (50%) and the left VF was paralyzed in the other five patients (50%).

All patients underwent percutaneous injection laryngoplasty for the paralyzed vocal fold; Radiesse (CaHA) was the injecting material in nine patients (90%) whereas Perfectha deep (hyaluronic acid) was used in only one patient (10%). The amount of injectate used was 1.5 ml in three patients (30%), while the remaining seven cases (70%) consumed 0.75 ml. Descriptive and demographic data were summarized in Table 1.

Follow-up data was missed in one patient who was from Sudan and returned to his country next day after injection. Stroboscopic evaluation for four patients could not be done 3 months post-injection due to technical problems (the instrument was out of function). Regarding swallowing, neither of the patients showed penetration/aspiration or residue on pre-injection VFSS; therefore, swallowing evaluation was not conducted post-injection.

Two of the patients needed voice therapy as a further management post-injection, and only one of them was compliant to training and received 33 sessions of voice treatment.

Injection laryngoplasty outcomes

Subjective voice outcomes

The office-based VF injection improved the patients' APA of voice quality (overall grade and breathy characters) and patients' satisfaction of their voices as assessed by modified GRBAS scale and VHI respectively. This was clear from the significant difference between pre-injection and all post-injection results. This improvement was stable throughout the follow-up period as comparison between post-injection results revealed non-significant difference (Tables 2 and 3).

Objective voice outcomes

The results demonstrated that the size of glottic gap decreased in both post-injection assessments. The pre-injection median value was IV then decreased to II 1 week post-injection and became III 3 weeks post-injection. Such improvement was more obvious in the 1st follow up as confirmed by significant difference between pre-injection and 1 week post-injection measures of the glottic gap. Improvement was also noticed when comparing the pre-injection and the 3 months post-injection measures; however, it was statistically non-significant (Table 4).

Both jitter and shimmer showed satisfactory improvement post-injection. The median value of jitter was 1.29% pre-injection and decreased to 0.46% 1 week post-injection. This improvement was sustained 3 months post-injection as the median value of jitter was 0.46%. The pre-injection median value of shimmer was 10.65% then decreased to 4.43% 1 week post-injection and it was 3.14% 3 months post-injection. This indicated quite improvement in both parameters, and it was confirmed by significant difference between pre-injection and all post-injection results. This improvement continued throughout the follow-up period as the comparison between post-injection values of both jitter and shimmer revealed non-significant difference. There was evident improvement in the H/N ratio. This was confirmed by significant difference between pre-injection and the 1 week post-injection results. On the other hand, comparison between pre-injection and the 3 months post-injection values revealed statistically non-significant difference (Table 5).

MPT was sufficiently increased following injection; its pre-injection median value was 3.28 s and increased to 7 s 1 week post-injection then became 7.1 s 3 months post-injection. This improvement was consistent throughout the follow-up periods. This was observable from significant difference between pre-injection and post-injection scores as demonstrated in Table 5.

Table 1 Descriptive and demographic data of the patients

Patient number	Age	Gender	Etiology of paralysis	Duration of dysphonia	Injection material	Side of paralysis	Amount of injection
1	30	M	Post-thyroidectomy	1 year	Radiesse	Right	0.75 ml
2	41	F	Post-thyroidectomy	7 months	Radiesse	Right	0.75 ml
3	57	F	Post-thyroidectomy	1 year	Radiesse	Left	0.75 ml
4	28	F	Thoracic surgery	1 ½ year	Radiesse	Left	0.75 ml
5	55	F	Post-thyroidectomy	2 years	Radiesse	Right	0.75 ml
6	20	M	Idiopathic	5 years	Radiesse	Left	0.75 ml
7	41	F	Post-thyroidectomy	7 months	Radiesse	Right	0.75 ml
8	42	F	Idiopathic	3 months	Hyaluronic acid	Right	1 ml
9	60	M	Idiopathic	7 months	Radiesse	Left	1.5 ml
10	45	M	Idiopathic	1 year	Radiesse	Left	1.5 ml

Table 2 Comparison between pre-injection and post-injection results of the grade and breathy character of dysphonia ($n = 9$)

GRBAS scale	Grades	Pre-injection Number of patients (%)	1 week post-injection Number of patients (%)	3 months post-injection Number of patients (%)	Chi-square test
Overall grade of dysphonia	0	0	2(22.2)	3(33.3)	P1 = 0.01* P2 = 0.024* P3 = 0.6
	I	1(11.1)	6(66.7)	4(44.4)	
	II	4(44.4)	0	2(22.2)	
	III	4(44.4)	1(11.1)	0	
	Median value	II	I	I	
Breathy character	0	0	2(22.2)	3(33.3)	P1 = 0.01* P2 = 0.024* P3 = 0.6
	I	1(11.1)	6(66.7)	4(44.4)	
	II	4(44.4)	0	2(22.2)	
	III	4(44.4)	1(11.1)	0	
	Median value	II	I	I	

*P value < 0.05 is significant, P value > 0.05 non-significant, *P1* pre-injection versus 1 week post-injection, *P2* pre-injection versus 3 months post-injection, *P3* 1 week post-injection 1 versus 3 months post-injection

Laryngostroboscopic parameters

Both phase closure and phase symmetry showed statistically significant improvement in both follow-ups as compared to pre-injection. On the other hand, comparing pre-injection and post-injection results of amplitude, mucosal wave, and ventricular folds revealed non-significant difference as demonstrated in Table 6.

Pulmonary function tests (PFTs)

Comparison between predicted values of PFT and pre-injection values revealed non-significant difference ($P > 0.05$) except for both PEF and FEV/PEF values ($P < 0.05$). However, comparison between pre-injection and post-injection results revealed non-significant difference in all spirometric measures, as illustrated in Table 7.

Perioperative complications

One patient had difficulty in tolerating the procedure because of gagging; however, this was overcome by increasing dose of local anesthesia. None of the patients developed stridor. One patient had minimal bleeding in the injected vocal fold, but it was resolved spontaneously within 1 week without any sequelae.

Discussion

Vocal fold injection is an established procedure that has been widely used for decades. A new era has evolved in the field of injection due to sophisticated technologies (as regards visualization and materials) and novel injection approaches [12]. Office-based techniques gained superiority over direct laryngoscopy approach as they render direct feedback of VF closure and voice outcome during injection. Also, avoidance of general anesthesia and its hazards is one of the merits of the awake procedure [12].

The present study aimed at evaluating respiratory and voice outcomes of office-based injection laryngoplasty in patients with UVFP. The study was conducted on 10 patients with UVFP (4 males and 6 females) in the age range 20–60 years. Iatrogenic cause was the cause of VFP in the majority of patients (60%) followed by idiopathic cause (40%). This finding is close to that reported by a number of previous studies such as Morgan et al. [21], Rudolf and Sibylle [22], and Mattioli et al. [23] who also concluded that iatrogenic causes including thyroidectomy and thoracic surgery were the commonest causes of VFP.

Choosing the injecting material was based on duration of dysphonia reported by the patients. In the nine patients who were dysphonic for more than 6 months (with range 7 months–5 years), Radiesse was chosen as it is long-acting material and the chance of spontaneous recovery in these patients is low. As stated by Issihiki [24] and Kotby et al. [25], the chance of the VF to

Table 3 Comparison between pre-injection and post-injection results of the VHI

VHI percentile values	Pre-injection scores	1 week post-injection scores	3 months post-injection scores	Test of significance	
25th	54	22	28	Friedman	Wilcoxon
50th (median)	82	45	40	$\chi 2 = 7.3$	P1 = 0.025*
75th	96	76	60	$P =$	P2 = 0.015*
				0.025*	P3 = 0.59

Friedman test was used for non-parametric data, $\chi 2$ Pearson's chi-square, Wilcoxon test is used to compare each 2 measures, *P value < 0.05 is significant, P value > 0.05 non-significant, *P1* pre-injection versus 1 week post-injection, *P2* pre-injection versus 3 months post-injection, *P3* 1 week post-injection 1 versus 3 months post-injection

Table 4 Pre-injection and post-injection follow ups of the glottic gap (n = 9)

Grade of glottic gap	Pre-injection Number of patients (%)	1 week post-injection Number of patients (%)	3 months post-injection Number of patients (%)	Chi-square test
0	0	1(11.1%)	1(11.1%)	P1 = 0.014* P2 = 0.186 P3 = 0.8
I	0	3(33.3%)	2(22.2%)	
II	2(22.2%)	2(22.2%)	1(11.1%)	
III	1((11.1%)	3(33.3%)	3(33.3%)	
IV	6(66.7%)	0	2(22.2%)	
Median value	IV	II	III	

Chi-square test was used to compare between each two groups, *P* value < 0.05 is significant, *P* value > 0.05 non-significant, *P1* pre-injection versus 1 week post-injection, *P2* pre-injection versus 3 months post-injection, *P3* 1 week post-injection 1 versus 3 months post-injection

restore its mobility after 6 months is null. One patient only was dysphonic for 3 months, for whom hyaluronic acid was the substance of choice as it has temporary action (its effect may last up to 6 months).

Subjective and objective voice assessments, as well as pulmonary function tests pre- and post-injection were done. Apart from Sudanese patient, follow-up data were obtained twice for 9 patients; 1 week and 3 months post-injection. Unfortunately, technical problems did not permit stroboscopic evaluation of 4 patients 3 months post-injection.

The office-based VF injection improved the patients' APA of voice as assessed by modified GRBAS scale and showed satisfactory improvement after injection. This was evident from the significant difference between pre-injection and post-injection results. These results are consistent with Woo et al. [26] and Powell et al. [27] studies. The patients in the present study reported significant improvement in their perceived voice in the 1st follow-up (after 1 week), and this improvement continued after 3 months as reported in the 2nd follow-up as evident from their VHI scores. These results come in agreement with Mohammed et al. [28] and Mattioli et al. [23] who also reported significant improvement in both immediate and long term follow-up assessments.

As regards the size of the glottic gap, results showed statistically non-significant decrease 3 months post-injection; this could be explained by the small sample size of patients enrolled in the study. The median grade of glottic gap was IV before injection, II 1 week after injection and III 3 months after injection. These results can be explained by the small sample size over 2 years of the study. The increase in the size of glottic gap after 3 months period could be attributed to partial resorption of the material and the possible need for overcorrection of glottic gap through increasing the dose of the injectate.

Table 5 Pre-injection and post-injection follow ups of acoustic and aerodynamic analysis

Acoustics and aerodynamics		Percentiles	Pre-injection scores	1 week post-injection scores	3 months post-injection scores	Test of significance	
Acoustic parameters	Shimmer (%)	25th 50th 75th	7.47 10.65 20.2	2.8 4.43 8.78	2.15 3.14 8.53	Friedman $\chi 2$ = 8.6 *P* = 0.013*	Wilcoxon P1 = 0.02* P2 = 0.008* P3 = 0.67
	Jitter (%)	25th 50th 75th	0.76 1.29 3.6	0.42 0.46 0.91	0.41 0.69 0.87	Friedman $\chi 2$ = 13.5 *P* = 0.001*	Wilcoxon P1 = 0.008* P2 = 0.008* P3 = 0.76
	H/N ratio (dB)	25th 50th 75th	6 11.8 18.6	13 20 22.4	9.8 17.8 20.8	Friedman $\chi 2$ = 8.2 *P* = 0.016*	Wilcoxon P1 = 0.015* P2 = 0.1 P3 = 0.86
Aerodynamics	MPT (s)	25^{th} 50^{th} 75^{th}	2.65 3.28 5.65	3.7 7 10.23	4.25 7.1 10.25	Friedman $\chi 2$ = 14 *P* = 0.001*	Wilcoxon P1 = 0.008* P2 = 0.008* P3 = 0.37

Friedman test was used for non-parametric data, $\chi 2$ Pearson's chi-square, Wilcoxon test is used to compare each 2 measures, *P value < 0.05 is significant, P value > 0.05 non-significant, *P1* pre-injection versus 1 week post-injection, *P2* pre-injection versus 3 months post-injection, *P3* 1 week post-injection 1 versus 3 months post-injection

Table 6 Comparison between pre-injection and post-injection results of stroboscopic parameters

Stroboscopic parameters	Grade	Pre-injection Number of patients (%)	1 week post injection Number of patients (%) (*N* = 9)	3 months post injection Number of patients (%) (*N* = 5)	Chi square test was used.
Mucosal wave of paralyzed VF.	**I**	3(33.3)0	7(77.8)	4(80)	P1 = 0.2
	II	5(55.6)	1(11.1)	1(20)	P2 = 0.36
	III	1(11.1)	1(11.1)	-	P3 = 1
	Median value	**II**	**I**	**I**	
Amplitude of paralyzed VF	**I**	2(22.2)	6(66.7)	4(80)	P1 = 0.15
	II	7(77.8)	3(33.3)	1(20)	P2 = 0.09
	Median value	**II**	**I**	**I**	P3 = 1
Phase closure	**I**	0	8(88.9)	4(80)	P1 < 0.001**
	III	9(100)	1(11.1)	1(11.1)	P2 = 0.005*
	Median value	**III**	**I**	**I**	P3 = 1
Phase symmetry.	**I**	0	7(77.8)	4(80)	P1 = 0.003*
	II	8(88.9)	2(22.2)	1(20)	P2 = 0.006*
	III	1(11.1)	0	0	P3 = 1
	Median grade	**II**	**I**	**I**	
Ventricular folds	**I**	4(44.4)	4(44.4)	2(40)	P1 = 1
	II	5(55.6)	5(55.6)	3(60)	P2 = 1
	Median value	**II**	**II**	**II**	P3 = 1

Chi-square test was used to compare between each two measures, *P* value < 0.001 highly significant, **P* value < 0.05 is significant, *P* value > 0.05 non-significant, *P1* pre-injection versus 1 week post-injection, *P2* pre-injection versus 3 months post-injection, *P3* 1 week post-injection 1 versus 3 months post-injection

Maximum phonation time is a good functional measure of glottal competence [29]. It is highly sensitive to glottic insufficiency as its values tend to decrease with increasing size of glottic gap [30]. Jitter and shimmer refer to frequency and amplitude variation, respectively, from cycle to cycle of sound wave [31]. Decreasing perturbation of frequency and amplitude of sound wave implies better periodicity and symmetry in glottic wave vibration which in turn indicates better APA of voice. Office-based injection of our patients led to significant decrease in the values of jitter and shimmer, and significant increase in MPT and H/N ratio, when comparing pre-injection to post-injection results.

Considering laryngostroboscopic results, both phase closure and phase symmetry showed significant improvement in both follow-ups after injection. This can be attributed to approximating the paralyzed VF to the normal one which would increase the number of closed phases within the vibratory cycles. In spite of the non-significant difference regarding mucosal wave, there was a trend toward clinical improvement noticed in our results especially in the 1 week follow-up. The small sample size might have hindered this clinical improvement to reach statistical significance.

Kashima [32] and Cantarella et al. [33] measured respiratory flows in patients with UVFP using flow-volume loop spirometry and reported variable extrathoracic obstruction with significantly reduced inspiratory flows in their patients. The position of the paralyzed vocal fold was not related to the severity of the obstruction. Kashima [32] hypothesized that the flaccid paralytic fold is sucked into the airstream during inspiration, causing dynamic upper airway narrowing whereas forced expiration laterally displaces the paralyzed vocal fold causing a passive widening of the glottic aperture. Janas et al [34] mentioned that none of their UVFP patients demonstrated symptoms of laryngeal obstruction, but 17% of them showed subclinical evidence of obstruction on flow volume loops.

Results of the present study revealed that pre-injection PEF scores were significantly reduced when compared to the predicted values, a finding that coincides with that of Cantarella et al. [35]. On the other hand, non-significant differences were found between the predicted values and

Table 7 Comparison between pre-injection and post-injection results of spirometry

Spirometric measures	Percentile values	Predicted values	Pre-injection scores	1 week post-injection scores	3 months post-injection scores	Predicted vs pre-injection	Pre–post injection comparisons
						MW	Friedman
FVC in liters	25th	2.99	2.12	2.35	2.45	$Z = 1.15$	$\chi2 = 1.55$
	50th	3.39	2.9	2.98	3	$P = 0.25$	P = 0.45
	75th	4.39	4.1	4.38	4.9		
						MW	Friedman
FEV in liters	25th	2.6	1.79	1.85	2.13	$Z = 1.19$	$\chi2 = 0.89$
	50th	2.99	2.61	2.46	2.42	$P = 0.23$	$P = 0.64$
	75th	3.67	3.66	3.67	3.78		
						MW	Friedman
PEF in liters/second	25th	6.3	3.3	3.85	3.5500	$Z = 2.6$	$\chi2 = 0.67$
	50th	6.6	4.27	4.95	4.2400	$P = 0.009$*	$P = 0.7$
	75th	7.6	5.87	5.745	5.7500		
FEV/FVC in %	Mean	80.9	85.3	81.6	83.1	$T = 1.4$[a]	$F = 0.26$[a]
	SD	2.5	8.9	10.3	11.8	$P = 0.18$	$P = 0.7$
FEV/PEF	Mean	0.43	0.59	0.59	0.63	$T = 3.4$[a]	$F = 0.3$[a]
	SD	0.07	0.12	0.15	0.3	$P = 0.004$*	$P = 0.6$

Friedman test was used for non-parametric data
[a]One-way ANOVA test for normally distributed data
[b]Independent *t* test for normally distributed data, *MW* Mann-Whitney test non-parametric data, *χ2* Pearson's chi-square

the pre-injection scores of FEV_1. Similarly, Empey [36] observed the discrepancy between a markedly decreased PEF in the presence of a normal FEV_1 in patients with variable upper airway obstruction. He proposed a simple index of FEV_1/PEF for the assessment of upper airway obstruction with a value > 10 mL/L/min indicating significant obstruction.

The non-significant difference in all spirometric measures between pre- and post-injection is in line with the result of Asik et al. [37] who utilized hyaluronic acid injection in their patients and indicates that VF injection had no effect on respiratory status of the patients which is important for the patients' quality of life and patients' satisfaction.

Using Teflon and fat injections respectively, Cormier et al. [38] and Cantarella et al. [35] also reported that VF augmentation has not worsened upper airway obstruction and did not affect spirometric values and even improved inspiratory airflows. The latter finding was attributed to the induced stiffening of the paralyzed vocal fold preventing the flaccid fold from moving toward the midline during inspiration.

To the best of our knowledge, this study is the first to investigate the effect of Radiesse injection in UVFP patients on respiratory function and can be considered as an exploratory clinical trial that demonstrates its safety and promising role in the management of these patients.

Conclusion

Office-based injection laryngoplasty is a safe and effective method for treating UVFP. Patients with glottic gap (< 1–3 mm) are perfect candidates for such procedure. Radiesse is a safe and effective injecting material. Transcutaneous cricothyroid approach is a perfect method to perform the injection. However, it may be difficult with gagging patients. Injection laryngoplasty improves patients' voice quality and does not impair respiration. The duration of VFP should be put into consideration when choosing the suitable injecting material. Overcorrection of the paralyzed VF is recommended to achieve better outcomes. We recommend replicating the study on a larger sample with longer follow-up duration to evaluate long-term benefits for these patients and to get more conclusive results regarding the effect of injection laryngoplasty on pulmonary function.

Abbreviations

VF: Vocal fold; VFP: Vocal fold paralysis; UVFP: Unilateral vocal fold paralysis; FVC: Forced vital capacity; FEV_1: Forced expiratory volume in 1 sec.; CaHA: Calcium hydroxylapatite; VHI: Voice Handicap Index; APA: Auditory perceptual assessment; MPT: Maximum phonation time; VFSS: Videofluoroscopic swallowing study; H/N: Harmonic to noise

Acknowledgements

We (all the authors) wish to thank all patients who participated in this research, and our colleagues in ENT Department and Phoniatric Unit in Mansoura University.

Authors' contributions
All authors contributed to the study conception and design, and patient selection. Injection of cases, data analysis, and interpretation were performed by AE, OA, and TA. Analysis of spirometric data was done by TE. Manuscript writing was mainly performed by AE. OA shared in writing and reviewing the manuscript, and submit the manuscript for publication. WM and TA contributed to reviewing and editing the manuscript. The authors read and approved the final manuscript.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials
All datasets used are available.

Ethics approval and consent to participate
The study protocol has been approved by the IRB committee of Mansoura Faculty of Medicine, Mansoura University, Egypt (MS/15.2.20). The procedure carried out in the study is an accepted part of the main routine clinical assessment and management of cases of voice disorders. It was conducted in accordance with the principles of the Declaration of Helsinki. The protocol is minimally invasive and clinically sound. Procedure was fully explained to the patients. A written informed consent was signed by all the participants prior to any examination and injection.

Consent for publication
It was included in the written consent to participate in the study by the participants.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Phoniatric Unit, ORL Department, Faculty of Medicine, Mansoura University, Mansoura 35516, Egypt. [2]ORL Department, Faculty of Medicine, Mansoura University, Mansoura 35516, Egypt. [3]Chest Medicine Department, Faculty of Medicine, Mansoura University, Mansoura 35516, Egypt.

Received: 23 September 2020 Accepted: 27 November 2020
Published online: 07 January 2021

References

1. Kupfer RA, Meyer TK (2014) Evaluation of unilateral vocal fold immobility. Curr Otorhinolaryngol Rep 2(2):105–113
2. Rosen CA, Simpson CB (2008) Operative techniques in laryngology. Germany: Springer-Verlag Berlin Heidelberg.
3. Lablance GR, Maves MD (1992) Acoustic characteristics of post-thyroplasty patients. Otolaryngol Head Neck Surg 107(4):558–563
4. Sulica L, Blitzer A (2006) Vocal fold paralysis. Springer-Verlag, Berlin/Heidelberg
5. Brunner E, Friedrich G, Kiesler K, Chibidziura-Priesching J, Gugatschka M (2011) Subjective breathing impairment in unilateral vocal fold paralysis. Folia Phoniatr Logop 63(3):142–146
6. Paine NJ, Joseph MF, Bacon SL, Julien CA, Cartier A, Ditto B, Favreau H, Lavoie KL (2019) Association between depression, lung function, and inflammatory markers in patients with asthma and occupational asthma. J Occup Environ Med 61(6):453–460
7. Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R et al (2005) General considerations for lung function testing. Eur Respir J 26:153–161
8. GOLD (2013) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Global initiative for chronic obstructive lung disease http://www.goldcopd.org/uploads/users/files/GOLD_Report_2013_Feb20.pdf
9. Bassiouny S (1998) Efficacy of the accent method of voice therapy. Folia Phoniatr Logop 50(3):146–164
10. Zeng T, Zhang Z, Peng W, Zhang F, Shi BY, Chen F (2017) Unilateral laryngeal pacing system and its functional evaluation. Neural Plast 2017: 8949165
11. Lasso JM, Poletti D, Scola B, Vilda PG, Martín AI, Santos ME (2018) Injection laryngoplasty using autologous fat enriched with adipose-derived regenerative stem cells: a safe therapeutic option for the functional reconstruction of the glottal gap after unilateral vocal fold paralysis. Stem Cells Int 2018:8917913
12. Mallur PS, Rosen CA (2010) Vocal fold injection: review of indications, techniques, and materials for augmentation. Clin Exper Otorhinolaryngol 3:177–182
13. Bove MJ, Jabbour N, Krishna P, Flaherty K, Saul M, Wunar R et al (2007) Operating room versus office-based injection laryngoplasty: a comparative analysis of reimbursement. Laryngoscope 117(2):226–230
14. Carroll TL, Rosen CA (2011) Long-term results of calcium hydroxylapatite for vocal fold augmentation. Laryngoscope 121(2):313–319
15. Lodder WL, Dikkers FG (2015) Comparison of voice outcome after vocal fold augmentation with fat or calcium hydroxylapatite. Laryngoscope 125(5): 1161–1165
16. El-Badrawy AR, El-Hoshy HM, Sheikhany AR, El-Rehim WS (2019) Comparison between functional outcomes in patients with unilateral vocal fold paralysis undergoing injection laryngoplasty under general anesthesia versus local anesthesia. Egyptian J Otolaryngol 35:92–102
17. Kotby M (1986) Voice disorders: recent diagnostic advances. Egypt J Otolaryngol 3(10):69–98
18. Malki KH, Mesallam TA, Farahat M, Bukhari M, Murry T (2010) Validation and cultural modification of Arabic voice handicap index. Eur Arch Otorhinolaryngol 267(11):1743–1751
19. Lu FL, Casiano RR, Lundy DS, Xue J-W (1996) Longitudinal evaluation of vocal function after thyroplasty type I in the treatment of unilateral vocal paralysis. Laryngoscope 106(5):573–577
20. Teixeira JP, Oliveira C, Lopes C (2013) Vocal acoustic analysis - jitter, shimmer and HNR parameters. Procedia Technol 9:1112–1122
21. Morgan JE, Zraick RI, Griffin AW, Bowen TL, Johnson FL (2007) Injection versus medialization laryngoplasty for the treatment of unilateral vocal fold paralysis. Laryngoscope 117(11):2068–2074
22. Rudolf R, Sibylle B (2012) Laryngoplasty with hyaluronic acid in patients with unilateral vocal fold paralysis. J Voice 26(6):785–791
23. Mattioli F, Bettini M, Botti C, Busi G, Tassi S, Malagoli A et al (2017) Polydimethylsiloxane injection laryngoplasty for unilateral vocal fold paralysis: long-term results. J Voice 31(4):517.e1–517.e7
24. Isshiki N (1991) Laryngeal framework surgery. Adv Otolaryngol Head Neck Surg 1(5):37
25. Kotby MN, Abdel-Rahman AG, Saleh MM, El-Assal NN, Al-Malki KH (2003) Evaluation of vocal fold fat augmentation in management of paralytic glottal gap. PhD Faculty of Medicine, Ain Shams, Cairo
26. Woo SH, Son Y-I, Lee SH, Park JJ, Jp K (2013) Comparative analysis on the efficiency of the injection laryngoplasty technique using calcium hydroxyapatite (CaHA): the thyrohyoid approach versus the cricothyroid approach. J Voice 27(2):236–241
27. Powell J, Carding P, Birdi R, Wilson JA (2014) Injection laryngoplasty in the outpatient clinic under local anaesthetic: a case series of sixty-eight patients. Clin Otolaryngol 39(4):224–227
28. Mohammed H, Masterson L, Gendy S, Nassif R (2016) Outpatient-based injection laryngoplasty for the management of unilateral vocal fold paralysis - clinical outcomes from a UK centre. Clin Otolaryngol 41(4):341–346
29. Benninger MS, Crumley RL, Ford CN, Gould WJ, Hanson DG, Ossoff RH et al (1994) Evaluation and treatment of the unilateral paralyzed vocal fold. Otolaryngol Head Neck Surg 111:497–508
30. Hirano M, Koike Y, von Leden H (1968) Maximum phonation time and air usage during phonation. Clinical study. Folia Phoniatr 20:185–201
31. Zwetsch IC, Fagundes RDR, Russomano T, Scolari D (2006) Digital signal processing in the differential diagnosis of benign larynx diseases [abstract in English]. Sci Med 16(3):109–114
32. Kashima HK (1984) Documentation of upper airway obstruction in unilateral vocal cord paralysis: flow-volume loop studies in 43 subjects. Laryngoscope 94:923–937
33. Cantarella G, Fasano V, Bucchioni E, Domenichini E, Cesana BM (2003) Spirometric and plethysmographic assessment of upper airway obstruction in laryngeal hemiplegia. Ann Otol Rhinol Laryngol 112:1014–1020
34. Janas JD, Waugh P, Swenson ER, Hillel A (1999) Effect of thyroplasty on laryngeal airflow. Ann Otol Rhinol Laryngol 108:286–292
35. Cantarella G, Fasano V, Maraschi B, Mazzola RF, Sambataro G (2006) Airway resistance and airflow dynamics after fat injection into vocal folds. Ann Otol Rhinol Laryngol 115:810–815

36. Empey DW (1972) Assessment of upper airways obstruction. Br Med J 3(5825):503–505
37. Asik MB, Karasimav O, Birkent H, Merati AL, Gerek M, Yildiz Y (2015) Airway and respiration parameters improve following vocal fold Medialization: a prospective study. Ann Otol Rhinol Laryngol 124(12):972–977
38. Cormier Y, Summer W, Menkes H (1978) Airflow in unilateralvocal cord paralysis before and after Teflon injection. Thorax 33:57–61

Publisher's Note