Efficacy of a Single Dose of Basic Fibroblast Growth Factor: Clinical Observation for 1 Year

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Summary: Objective. Basic fibroblast growth factor promotes wound healing by accelerating healthy granulation and epithelialization. However, the duration of the effects of a single intracordal injection of basic fibroblast growth factor has not been established, and administration intervals and timing have yet to be standardized. Here, we administered a single injection to patients with insufficient glottic closure and conducted follow-up examinations with high-speed digital imaging to determine the duration of the treatment response.

Study Design. Case series.

Methods. For treatment, 20 μg/mL recombinant human basic fibroblast growth factor was injected into two vocal cords. The following examinations were performed before the procedure and at 3-month intervals for 12 months starting at 1 month postinjection: Grade, Roughness, Breathiness, Asthenia, and Strain (GRBAS) scale assessment, maximum phonation time, acoustic analysis, high-speed digital imaging, glottal wave analysis, and kymographic analysis.

Results. Postinjection, the GRBAS scale score decreased, and the maximum phonation time was prolonged. In addition, the mean minimum glottal area and mean minimum glottal distance decreased. These changes were significant at 12 months postinjection compared with preinjection. However, there were no significant changes in the vibrations of the vocal cord margins.

Conclusions. The intracordal injection of basic fibroblast growth factor improved insufficient glottic closure without reducing the vibrations of the vocal cord margins. This effect remained evident at 12 months postinjection. A single injection can be expected to yield a sufficient and persistent long-term effect.

Key Words: Basic fibroblast growth factor–Vocal cord injection–High-speed digital imaging–Glottal insufficiency–Long-term effect.

INTRODUCTION

Materials such as silicone,[1] autologous fat,[2,3] fascia,[4] and atelocollagen[5,6] have been injected into the vocal cords to manage diseases involving vocal cord atrophy. However, these materials do not always elicit a satisfactory effect. Basic fibroblast growth factor (bFGF), discovered in 1974, promotes the migration of fibroblasts[7] and is used in Japan to treat intractable decubitus ulcers and other diseases. This factor acts on wounds to promote the proliferation of keratinocytes and mesodermal cells, including vascular endothelial cells, fibroblasts, and vascular smooth muscle cells; these cells accelerate wound-healing effects such as angiogenesis, granulation, and epidermis formation.[8,9]

In 2004, Hirano et al found that injection of bFGF into the vocal cords of dogs and rats improves healing of vocal cord wounds by increasing the production of hyaluronic acid by fibroblasts in the vocal cord mucosa.[10,11] In two other studies, intravocal cord injection of bFGF in patients with vocal cord atrophy has been shown to improve voice quality and vocalization function.[12,13] These clinical trials verified the effects of multiple injections of bFGF. However, determining the optimal treatment regimen for bFGF injections, including the number of injections and the interval between injections, has been challenging. Although the use of fewer injections would be less invasive to the patient, the effects of a single injection remain unclear.

Laryngeal stroboscopy is commonly used to evaluate oscillation of the vocal cords. However, this method evaluates only apparent oscillation and is therefore not suited for precise evaluations. On the other hand, high-speed digital imaging (HSDI) is becoming more common and can be used to evaluate vocal cord oscillation at a very high level of precision.

In the present study, we aimed to examine the effects of a single bFGF injection to facilitate the development of standardized protocols for vocal cord treatment. We further analyzed the effects of this treatment using HSDI in follow-up examinations.

MATERIALS AND METHODS

Patients

The patients in this study had diseases involving insufficient glottic closure and were treated as outpatients at the Otolaryngology Department of Nihon University Hospital. The study was explained to the patients, and intracordal injections were administered to 17 patients (eight men, nine women; mean age, 69.18 years) who consented to the treatment. Seven patients had aging-related atrophy, six patients had sulcus vocalis, and four patients had recurrent laryngeal nerve paralysis. Patients with recurrent laryngeal nerve paralysis underwent type 1 thyroplasty and arytenoid adduction before injection. None of the patients

Accepted for publication September 29, 2015.

Funding: This work was supported by JSPS KAKENHI Grant Number 23592540. The authors have no other funding or financial relationships to disclose.

Conflict of interest: None.

This study was presented at the Combined Otolaryngology Spring Meeting of the American Laryngological Association in Boston, MA, on April 22–26, 2015.

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Journal of Voice, Vol. ■■, No. ■■, pp. ■■-■■

0892-1997

http://dx.doi.org/10.1016/j.jvoice.2015.09.018

TABLE 1.
Clinical Characteristics of the Patients

Variable	Value (%)
Sex, n	
Male	10 (58.9%)
Female	7 (41.2%)
Age, years	69.18 ± 11.37
Diseases, n	
Aging-related atrophy	7 (41.2%)
Sulcus	6 (35.3%)
Recurrent laryngeal nerve paralysis	4 (23.5%)
Phonosurgery, n	4 (23.5%)
Smoking, n	3 (17.6%)
Alcohol, n	11 (64.7%)
Acid reflux, n	3 (17.6%)

had previously undergone phonosurgery. Three patients had a history of smoking and 11 had a history of alcohol consumption. In addition, three patients had previously experienced heartburn and were diagnosed with acid reflux (Table 1).

Surgical method

After inhaling 4% lidocaine, patients received surface anesthesia with 4% lidocaine in the laryngeal and pharyngeal mucosa. Intracordal bFGF injections were administered with a 25-gauge needle during observation of the area with transnasal fiberoptic laryngoscopy. Trafermin (Fiblast Spray 250; Kaken Co., Tokyo, Japan) was diluted to 20 μg/mL for injection. Both vocal cords were injected with 2–4 μg on each side. Injections were made into the superficial lamina propria in all patients, regardless of the underlying disease. Drug concentrations and the choice of the lamina propria as the injection site were based on a previous study by Hirano et al[11] The operator was not involved in the assessment of the parameters below.

Evaluation times and parameters

Preinjection assessments were done immediately before the injection. The following examinations were performed 1, 3, 6, 9, and 12 months after the procedure.

GRBAS scale

The Grade, Roughness, Breathiness, Asthenia, and Strain (GRBAS) scale expresses the severity of hoarseness and is widely used to evaluate auditory psychology.[14] We examined G, which evaluates overall hoarseness, and B, which reflects the breathiness of the hoarseness. These assessments were performed by three physicians each with at least 10 years of experience in outpatient vocal examination. The tests were conducted during conversation prior to confirming the patients' information and performing laryngeal fibroscopy.

Maximum phonation time

Maximum phonation time (MPT) was measured as aerodynamic examination. MPT was measured with patients in a seated position. Patients were verbally encouraged to produce a sustained vowel /a/ sound at a comfortable pitch and volume for as long as possible.

HSDI

An HSDI camera (FASTCAM MC2.1; Photron, Tokyo, Japan) was connected to a rigid endoscope (model 9016; Kaypentax, Montvale, NJ, USA) and light source (Kay Xenon 300-watt light source; Kaypentax). HSDIs were recorded during sustained phonation of the vowel /e/ at a comfortable frequency and comfortable intensity, and a sequence of stable vocal fold vibrations was selected for analysis. The imaging speed was 4000 frames per second. The images were taken in monochrome to preserve video contrast. Motion analysis software (*Kay Image Processing Software* model 9181; Kaypentax) was used for glottal wave analysis (GWA)[15] and kymographic analysis.[16–18] GWA was used to extract glottal area and the distance between the centers of the margins of the vocal cord membranes. The length of the vocal cord membrane was considered to be 100, and the units were the number of pixels. The mean minimum glottal area and minimum distance between the centers of the margins of the vocal cord membranes were evaluated (Figure 1). Cross-sections in three locations were used for kymographic analysis: midway between the anterior union and the centers of the vocal cord membranes (anterior glottis), at the centers of the membranes (central glottis), and midway between the centers of the membranes and the glottal protuberance (posterior glottis), as shown in Figure 2. For the evaluation of vocal cord vibration, the sine waves obtained from this analysis were used to measure the mean amplitudes of the left and right vocal cords.

Acoustic analysis

Voice samples were recorded at Nihon University in a quiet room in the Department of Otorhinolaryngology. A microphone that was supplied with the previously described HSDI camera system was attached to the camera and was used to record voice samples as the HSDIs were recorded. The task was explained and demonstrated to the patients before the recording. *Multi-Dimensional Voice Program* acoustic analysis software (MDVP, model 5105; Kaypentax) was used to analyze the voice data. Samples 0.5 seconds long, beginning when the voice stabilized, were recorded. The transition sections at the beginning and at the end of vocalization were excluded from the analysis. Period perturbation quotients (PPQs), amplitude perturbation quotients (APQs), and noise-to-harmonic ratios (NHRs) were measured.

Each of the samples was recorded only once. These recordings were analyzed by two physicians who were not present during the sample collection. The physicians were not provided with patient information, data sampling times, or any other information.

Statistical analysis

The GRBAS scale was analyzed with the Wilcoxon rank-sum test. All other outcome measures were analyzed with two-way ANOVA. Preinjection values were compared with their respective values at 1, 3, 6, 9, and 12 months postinjection. The level of statistical significance was set at $P < 0.05$. Statistical processing