Inflammatory complications of vocal fold injection with hyaluronic acid: a multiinstitutional study

Necat ENVER¹, Elad AZİZLİ²*, Sevtap AKBULUT³, Emel ÇADALLI TATAR⁴, Muhammed Kürrat YELKEN⁵, Kayhan ÖZTÜRK⁶, Hakan COŞKUN⁷, Ahmet Hakan BİRKEN⁵, Zahide Çiler BÜYÜKATALAY⁶, Ozan Bağış ÖZGÜRSOY⁶, Haldun ÖGUZ⁸

¹Department of Otolaryngology, Pendik Training and Research Hospital, Marmara University, İstanbul, Turkey
²Department of Otolaryngology, Private Practise, İstanbul, Turkey
³Department of Otolaryngology, Faculty of Medicine, Yeditepe University, İstanbul, Turkey
⁴Department of Otolaryngology, Dışkapı Yıldırım Beyazıt Research and Training Hospital, University of Health Sciences, Ankara, Turkey
⁵Department of Otolaryngology, Faculty of Medicine, Maltepe University, İstanbul, Turkey
⁶Department of Otorhinolaryngology, Medicana Konya Hospital, Faculty of Medicine, KTO Karatay University, Konya, Turkey
⁷Department of Otolaryngology, Faculty of Medicine, Bursa Uludağ University, Turkey
⁸Department of Otorhinolaryngology, Nişantaşı University, İstanbul, Turkey
⁹Department of Otorhinolaryngology Head and Neck Surgery, Faculty of Medicine, Ankara University Ankara, Turkey
¹⁰Department of Otolaryngology, Fonomer, Ankara, Turkey

* Correspondence: eladazizli@gmail.com

1. Introduction
Glottic insufficiency is one of the most common etiologic factors of dysphonia. Glottic insufficiency is usually secondary to unilateral vocal fold paralysis, unilateral or bilateral vocal fold paresis, sulcus vocalis, and presbylaryngitis. Injection laryngoplasty is a common therapeutic option for treatment of glottic insufficiency.

The purpose of injection is to gain adequate glottic closure to alleviate phonatory and swallowing symptoms [1]. Although several injectable substances have been in use for the larynx since the inception of injection laryngoplasty in 1911, the ideal one is yet to be found [2]. Hyaluronic acid (HA) is among the most commonly used substances for injection laryngoplasty. Its ease of
injection and unique properties in tissue regeneration, namely recruitment of fibroblasts, deposition of collagen, and improvement of the viscoelastic properties of the injected tissues, have made it a popular injectable material [3]. This naturally existing polysaccharide is found in the extracellular matrix of human cells and is also abundant in the vocal fold lamina propria. It is biocompatible and rarely induces foreign body reactions or cell-mediated immune responses. Clinical studies have supported the safety and efficacy of HA for vocal fold augmentation [4].

HA has been demonstrated as a safe material for vocal fold injection in the literature; however, most of these studies have small sample sizes. There has been case reports about inflammatory adverse reactions after vocal fold HA injections [5–7]. Recently, a study with a large sample size published the results from the assessment of 186 patients from a single institution [8]. In our study we aim to gather the clinical data of several institutions to understand the presentation and management of inflammatory adverse reactions of HA. The goal of our study is to identify the rate of complications and the adverse reactions after HA injection laryngoplasty in a multiinstitutional setting.

2. Materials and methods
A retrospective chart review of all patients from nine institutions who underwent vocal fold injection laryngoplasty with HA alone (Restylane, Galderma/Q-Med, Uppsala, Sweden) or HA with dextranomer (HA-D; Dexell, Istem Medikal, Ankara, Turkey) from January 2005 to September 2016 was performed. Injections were done either unilaterally or bilaterally in one session. The side and volume of injectable materials were decided according to clinical decision of the physician. A retrospective chart review was performed to identify patients with local complications. Patients with previous laryngeal surgery, vocal fold injections and patients with radiated neck were excluded from the study.

Demographic data, injection technique, type of injection material, the indication for injection, location of the procedure, and occurrence of complications were reviewed. Type, onset, and management of complications were also noted for patients with complications. Results were grouped according to the location of the procedure: under local anesthesia in the office setting (office group) or under general anesthesia in the operating room via direct microlaryngoscopy (OR group).

Complication rates were compared according to injection materials and the technique of injection. Statistical analysis of the study was performed using the MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium). The differences between groups were compared using the chi-squared test (or Fisher’s exact test when applicable).

3. Results
A total of 476 patients underwent laryngeal HA injection over an 11-year period in nine institutions. The average age of patients was 47.1 ± 13.7 years (range = 19–70), and the only indications were vocal fold paralysis (n = 417) and sulcus vocalis (n = 59). In all, 403 patients (84.6%) were injected with HA-D, and 73 (15.4%) were injected with HA only. The majority of injections were done under general anesthesia (OR group) (n = 382, 84.7%).

Complications were seen in nine patients. The mean age of patients with complications was 46.7 years (range = 36–57), and six of these patients were women. Five of the patients who experienced complications were in the OR group and received the injection under general anesthesia, whereas the remaining four were in the office group. There was no significant difference between complication rates in the office group and those in the OR group (P = 0.08). The main indication was unilateral vocal fold paralysis (n = 7), whereas two of the patients had sulcus vocalis. Although all the patients with complications were injected with HA-D, there was no statistically significant difference between patients who received HA and those who received HA-D (P = 0.220).

Five patients with complications presented mainly dyspnea, and the other four presented the chief complaint of dysphonia. The symptoms were observed postoperatively within the first 24 h in the majority of patients (n = 5). However, it was observed postoperatively on the second day in two patients, and on the third week in one patient. In videolaryngostroboscopic examination, the most common findings included hyperemia and edema of the vocal folds with or without false vocal folds, which were observed in seven patients, although the severity of these inflammatory findings varied (n = 7). Arytenoids were inflamed in five of these seven patients, and movements of the vocal folds were impaired in three of them, although their vocal folds were mobile preoperatively (Figures 1–3). In one patient, VLS examination revealed vocal fold hematoma that decreased mucosal wave and amplitude in one side of the larynx. In another patient, superficial deposition of the injected material on the vocal fold were noted, which also caused decreased mucosal wave and irregular closure in the affected vocal fold (Table).

Six of the patients with local inflammatory reaction received the treatments. Oral or parenteral corticosteroid was used as the main treatment in every patient who received treatment, and three of these patients received additional antibiotic treatment. Four of the patients needed 1 or 2 days of hospitalization. Two of them were kept under observation in the intensive care unit for 24 h; of these two patients, one underwent orotracheal intubation. All symptoms resolved between 2 days to 3 weeks in these patients.
Patients who demonstrated no signs of inflammation received no acute treatment or hospitalization. The patient with vocal fold hematoma was observed without treatment, and the hematoma resolved spontaneously in 2 weeks, completely preserving the integrity of mucosal wave and amplitude. However, the patient with superficial deposition of the injected material underwent microlaryngoscopic surgery for removal of the deposit 3 months later.

In our patient series of 476 individuals, the overall complication rate was 1.9%, (9/476), and the inflammatory complication rate was 1.47% (7/476). There was no difference in terms of inflammatory complication rates between office (n = 3) and OR (n = 4) groups (P = 0.142). Although all the inflammatory complications were only seen in HA-D injected patients, there was no statistically significant difference for these complications between patients treated with HA and those treated with HA-D (P = 0.309).

4. Discussion

HA is a commonly used material in injection laryngoplasty. However, it only lasts approximately 3 to 6 months [4]. In our patient series, two types of injection material were used: HA and HA-D. HA with dextranomer aims to increase the duration of the material with the permanence of the positive load of dextranomer. This form of HA is frequently used in urology for vesicoureteral reflux treatment [9]. No known inflammatory side effect with HA-D in urological practice has been documented in the recent literature [9]. Oguz et al. demonstrated the safety and efficacy of HA-D for laryngeal injections in a small group of patients [10]. Similarly, in our series, there was no significant difference for complication rates between HA and HA-D.

Injection laryngoplasty has been a workhorse in laryngology since it was first described by Brunings [2]. During the last century, with the improvements in general anesthetics, surgeons now prefer the operating room for injections. However, in the last 20 years, there has been a rising trend of in-office laryngeal injections [11]. The safety of the office-based injection is widely accepted in the literature [5,11]. In our study, only a small group of patients were injected in the office (n = 69, 14.5%), and four out of nine complications (44.4%) were experienced by patients who received office-based injections. There was no significant difference for overall complication rates between office-based injections and operating room injections in our series. Furthermore, for inflammatory complications, there was also no difference between these groups. Complication rates for injection laryngoplasty are very low, and to claim definitive conclusions, larger multiinstitutional studies are needed [5].
Complications that may be associated with vocal fold HA injection can be divided into two main groups: technical problems and inflammatory problems. Technical problems are related to the applied volume, application depth, and application area. Of the nine patients included in our series, two of them (22%; cases 3 and 9) experienced complications that could be considered as technical problems, such as hematoma and submucosal injection. Cases involving such technical problems have been described in the literature [7,8].

Besides the technical problems mentioned above, seven out of nine patients in our series experienced complications that can be classified as inflammatory. In animal studies, mild inflammation has been observed after vocal fold HA injection; however, no necrosis or granuloma formation has been observed [12]. In the literature, a few case series and case reports have indicated inflammatory adverse reactions following vocal fold HA injection [5–7]. In the largest series published by Dominguez et al., the incidence of inflammatory complications was 3.8%. In our patient group, this rate was 1.47% [8].

The onset of inflammatory reaction after vocal fold HA injection varies in the literature. Although in some of the series, there were patients whose symptoms started right after or several hours after injections [5,8], the most common onset time was 2 or 3 days after injection laryngoplasty in most of the series [7,8]. Very rarely, the start of the symptoms could be delayed for up to 3 weeks. Our results were similar with those recorded in the literature.

Table. Clinic data of the patients with complications.

| Case | Age | Sex | Approach   | Diagnosis     | Symptom                   | VLS Exam | Onset | Treatment                        | Interventions                                     | Resolution time |
|------|-----|-----|------------|---------------|---------------------------|----------|-------|----------------------------------|----------------------------------------------------|-----------------|
| 1    | 50  | M   | Transoral (GA) | UVFP | Dysphonia | Vocal fold edema (Figure 1) | 24 h     | Clinic follow-up | -                               | 2 weeks               |
| 2    | 44  | F   | Transoral (GA) | UVFP | Dysphonia | Vocal fold edema | 24 h | Antibiotic steroid (inhaler) | -                               | 60 days             |
| 3    | 42  | M   | Transoral (GA) | Sulcus vocalis | Dysphonia | Superior transposition of material | 0 h  | Clinic follow-up | 90th day surgery | 90 days            |
| 4    | 54  | F   | Transoral (GA) | UVFP | Dysphonia | Inflammation edema in FVF, arytenoid, and VF | 24 h | Antibiotic steroid | Intubation, ICU (1 day) | Hospitalization (totally 2 day) | 3 days          |
| 5    | 46  | F   | Thyrohyoid (LA) | Sulcus vocalis | Dyspnea | Inflammation edema in FVF, arytenoids, decreased VF motion | 3 weeks | Systemic steroid | 2 ED visit | 1-night hospitalization | 3 weeks         |
| 6    | 57  | M   | Transoral (GA) | UVFP | Dyspnea | Bilateral inflammation edema in FVFs, arytenoids, decreased VF motion | 0 h  | Systemic steroid | 2 days hospitalization (1-night ICU) | 4 days       |
| 7    | 36  | F   | Thyrohyoid (LA) | UVFP | Dyspnea | Inflammation edema in FVF, arytenoid | 72 h | Oral steroid and antibiotic | -                               | 1 week            |
| 8    | 55  | F   | Transoral (LA) | UVFP | Dyspnea | Inflammation edema in FVF, arytenoid (Figures 2 and 3) | 24 h | Systemic steroid | 2 days hospitalization | 2 day                |
| 9    | 37  | F   | Cricothyroid (LA) | UVFP | Dyspnea | Hematoma | 0 h  | Clinic follow-up | -                               | 2 days               |

GA: general anesthesia, LA: local anesthesia, UVFP: unilateral vocal fold paralysis, ICU: intensive care unit, VF: vocal fold, FVF: false vocal fold.
Various side effects associated with dermal HA injection have been described in the literature. These side effects include erythema, edema, and irritation to foreign body granuloma formation, ulceration, necrosis, and hypersensitivity reactions. The frequency of these side effects ranges between 0.06% and 0.8% in dermal applications [13,14]. HA may cause adverse inflammatory reactions through three main mechanisms: an ischemic event, an allergic or hypersensitivity reaction, or an acute infection of bacterial origin that causes inflammation with fluctuant and erythematous nodules [15].

Vasoconstriction may be one of the possible reasons for injections in the larynx because of a region limitation by cartilage from the lateral. In the case of overinjection, especially after radiotherapy, compression may occur in the vascular structures of the larynx, which may lead to ischemia. HA injections that cause vascular compression in dermal injections usually show an acute whitening followed by regional necrosis and ulceration in postoperative hours [13]. There is one report in the literature of a suspected compartment syndrome of the hemilarynx after injection with HA in a patient with a history of radiation [16]. Although patient with a history of neck radiotherapy was excluded in our study, there are no complications in this patient subgroup in Dominguez et al.'s series [8]. The injected volume of the material could be a factor leading possible cause of vascular compression. Unfortunately, there is data about the volume of the augmentation in our series. Even though in Dominguez study, the volume of injected materials in patients with inflammatory complication is within the range of average amount of injected HA, the relation between the amount of the injected HA and the inflammatory complication is not clearly understood yet.

Hypersensitivity due to bacterial proteins can be observed in relation to the production technique. HA-based injectable material contains very small amounts of protein, which can cause some reactivity. Currently, purification of HA fillers is considered to be more effective than before. However, the alleged reasons for hypersensitivity are less consistent. HA fillers might still contain trace amounts of protein contaminants even after purification. Therefore, hypersensitivity is still the most important pathophysiological cause [17].

In our patient series, HA-D was used for all patients with inflammatory complications. Inflammatory complication rates in our study were 1.9%. Although no statistical difference was demonstrated between HA-D and HA injections, it can be speculated that dextranomer may be the trigger for hypersensitivity. Even though no inflammatory side effects have been shown in the literature from urological practice, because of the location of the injection site, the possibility may be easily underestimated.

In the published clinical series by Dominguez et al., none of the augmentations include dextranomer or any other cationic substance. The inflammatory complication rate of their study (3.8%) [8]. was also similar to ours. Another case series of vocal fold HA injection demonstrated an inflammatory complication rate of 4.7% over 62 injections [18].

Infection is an important complication that must be avoided in dermal HA injections. This kind of complication is rare in dermal applications [16]. In patients with infection, increased white-blood-cell (WBC) and C-reactive protein (CRP), and/or abscess formation would be expected. Treatment with antibiotics and hyperbaric oxygen therapy after drainage has been demonstrated as an effective treatment approach. In cultures after abscess drainage, staphylococcal and streptococcal species were detected most frequently in facial application of HA [14].

Although none of the patients with complications exhibited WBC count elevation, empiric parenteral antibiotic therapy was initiated in all individuals with inflammatory findings in our patient group. This occurred because a significant proportion of patients applied with a disturbing complaint, such as dyspnea, and all possible treatment options were provided empirically.

In the literature, only one case of laryngeal abscess after vocal fold HA injection has been reported. In that case, the patient had a high WBC count and constitutional symptoms, and no organism was revealed in the microbiological culture and gram stain from the abscess sample. The patient's symptoms were relieved after drainage, systemic antibiotic, and corticosteroid therapy [15].

The most commonly used treatment among our patients was the corticosteroid. If it is accepted that inflammatory complications happen as a result of hypersensitivity reactions or infections, which are the most likely pathophysiological explanations, we can speculate that corticosteroids may have been helpful in decreasing edema and inflammation in our patients. Although none of the patients in our study had higher WBC or C-reactive protein, some of them also received empiric antibiotic treatment. In the facial application of HA, when a patient has an inflammatory reaction, antibiotics are widely used with hyaluronidase and corticosteroids [14]. Hyaluronidase would be beneficial to decrease bulkiness in overinjection complications; however, while working on the glottic level, it would cause an acute reduction in the size of the airway.

Surgery is also an option for patients with severe dyspnea resulting from HA injection. Tracheotomy may be needed in an advanced airway obstruction. In our series, only one patient with bilateral injection was intubated and hospitalized in intensive care for 1 day, but none of our
patients had a tracheotomy performed. Only one patient (case 3), who had transposition of injection material in the vocal fold, received surgical intervention in our study.

Although medical treatment and surgery are possible treatment options that can be offered for inflammatory complications of vocal fold injection, none of these treatments are evidence-based. Future studies are needed to clarify special treatment modalities for inflammatory complications of vocal fold injection.

To the best of our knowledge, our study is the largest vocal fold HA injection series ever published. Dominguez et al. published the results of 186 patients from a single institution [8]. Gathering and assessing complications from different institutions increases the possibility of identifying appropriate approaches to these rare complications.

Multinstitution retrospective studies have some disadvantages as well. It is not easily possible to standardize the treatment and management protocols. Each clinic has a different method of archiving patients’ data. This can limit the quality of information obtained from retrospective studies such as ours. Patients’ perceptual and acoustic voice analyses could be used in a prospective setting. Absence of patient-centered questionnaires was also another limitation of our study. These indices are widely used in laryngology clinics. They are especially useful to observe problems from patients’ perspective and to compare the results of different institutes.

**5. Conclusion**

Injection laryngoplasty with HA is a common therapeutic option for the treatment of glottic insufficiency. In our series, complications of all types were found to occur at a rate of 1.9%. Dyspnea and dysphonia were the common symptoms of complication most commonly starting after 1 day. Corticosteroid and antibiotic are the most accepted treatment by the authors of the study; HA can be considered a safe substance for vocal fold injections.

**Acknowledgement**

This study has presented in International Federation of Otolaryngology Societies (IFOS) 2017 Paris - ENT World Congress. June 24-28 2017 Paris, France.

**Conflict of interest**

All authors disclose that no any conflict of interest that may have influenced either the conduct or the presentation of the research.

**Informed consent**

The study protocol was approved by the institutional review board of Marmara University Medical Faculty, where the de-identified data were collected and analyzed, and by all contributing institutions administrations (Marmara University Clinical Researches Ethic Committee Ref No: 09.2019.301).

**References**

1. Song PC, Sung, CK, Franco RA. Voice outcomes after endoscopic injection laryngoplasty with hyaluronic acid stabilized gel. Laryngoscope 2010; 120 (Suppl. 4): S199. doi: 10.1002/lary.21666

2. Brunings W. Uber eine neue Behandlungs methode der Rekurrenslamung. Verhandl Ver Deutch Laryngologie 1911; 18: 93-98.

3. Thibeault SL, Klemuk SA, Chen X. Quinchia Johnson BH. In vivo engineering of the vocal fold ECM with injectable HA hydrogels-late effects on tissue repair and biomechanics in a rabbit model. Journal of Voice 2011; 25: 249-253. doi: 10.1016/j.jvoice.2009.10.003

4. Kim YS, Choi JW, Park JK, Kim YS, Kim H et al. Efficiency and durability of hyaluronic acid of different particle sizes as an injectable material for VF augmentation. Acta Oto-Laryngologica 2015; 135: 1311-1318. doi: 10.3109/00016489.2015.1070966

5. Halderman AA, Bryson PC, Benninger MS, Chota R. Safety and length of benefit of restylene for office-based injection medialization-a retrospective review of one institution's experience. Journal of Voice 2014; 28: 631-635. doi: 10.1016/j.jvoice.2014.01.010

6. Reiter R, Rudolf R, Brosch S, Sibylle B. Laryngoplasty with hyaluronic acid in patients with unilateral vocal fold paralysis. Journal of Voice 2012; 26: 785-791. doi: 10.1016/j.jvoice.2011.11.007

7. Traboulsi H, El Natout T, Skaff G, Hamdan AL. Adverse reaction to hyaluronic acid injection laryngoplasty: a case report. Journal of Voice 2017; 31: 245.e1-245.e2. doi: 10.1016/j.jvoice.2016.08.011

8. Dominguez LM, Tibbetts KM, Simpson CB. Inflammatory reaction to hyaluronic acid: a newly described complication in vocal fold augmentation. Laryngoscope 2017; 127: 445-449. doi: 10.1002/lary.26156

9. Tsai CC, Lin V, Tang L. Injectable biomaterials for incontinence and vesico-ureteral reflux: current status and future promise. Journal of Biomedical Materials Research Part B: Applied Biomaterials 2006; 77: 171-178. doi: 10.1002/jbm.b.30428

10. Oguz H, Demirci M, Arslan N, Arslan E. Long-term voice results of injection with hyaluronic acid-dextranomer in unilateral vocal fold paralysis. Acta Oto-Laryngologica 2013; 133: 513-517. doi: 10.3109/00016489.2012.750034
11. Sulica L, Rosen CA, Postma GN, Simpson B, Amin M et al. Current practice in injection augmentation of the vocal folds: indications, treatment principles, techniques, and complications. Laryngoscope 2010; 120: 319-325. doi: 10.1002/lary.20737

12. Perazzo PS, Duprat AC, Lancellotti CL. Histological behavior of the vocal fold after hyaluronic acid injection. Journal of Voice 2009; 23: 95-98. doi: 10.1016/j.jvoice.2007.05.006

13. DeLorenzi C. Complications of injectable fillers, part I. Aesthetic Surgery Journal 2013; 33: 561-575. doi: 10.1177/1097633813484492

14. DeLorenzi C. Complications of injectable fillers, part 2: vascular complications. Aesthetic Surgery Journal 2014; 34: 584-600. doi: 10.1177/1097633814525035

15. Enver N, Asya O, Abuzaid G, Gürol E. A very rare complication of hyaluronic acid injection for medialization laryngoplasty: a case with laryngeal abscess. Journal of Voice 2020; 34 (5): 812.e5-812.e8. doi: 10.1016/j.jvoice.2019.03.011

16. Shamanna SG, Bosch JD. Injection laryngoplasty: a serious reaction to hyaluronic acid. Journal of Otolaryngology - Head Neck Surgery 2011; 40: E39-42.

17. Abduljabbar MH, Basendwh MA. Complications of hyaluronic acid fillers and their managements. Journal of Dermatology & Dermatologic Surgery 2016; 20: 100-106. doi: 10.1016/j.jdds.2016.01.001

18. Hamdan AL, Khalifee E. Adverse reaction to restylane: a review of 63 cases of injection laryngoplasty. Ear Nose Throat Journal 2019; 98: 212-216. doi: 10.1177/0145561319835773