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ORIGINAL RESEARCH

Safety of percutaneous injection of bovine dermal crosslinked collagen for glottic insufficiency

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OBJECTIVE: Our aim was to review the safety of percutaneous injection laryngoplasty using bovine crosslinked collagen, focusing specifically on two often-stated concerns: injecting patients who are taking the anticoagulant medication warfarin, and injecting patients without prior skin hypersensitivity testing.

STUDY DESIGN AND SETTING: Retrospective chart review of injection laryngoplasty performed between 1997 and 2006 at the University of California, Los Angeles.

RESULTS: The study group consisted of 895 patients who underwent 1290 injection laryngoplasty procedures. No bleeding complications were noted in 59 patients taking warfarin. No allergic complications were reported in 845 patients who did not undergo skin hypersensitivity testing before injection laryngoplasty.

CONCLUSION: Percutaneous bovine crosslinked collagen injection laryngoplasty is safe in patients taking warfarin. Skin testing for hypersensitivity does not appear to be necessary before injection.

SIGNIFICANCE: Patients on warfarin are candidates for injection laryngoplasty without the need to discontinue the medication. Eliminating skin hypersensitivity testing before percutaneous bovine crosslinked collagen injection laryngoplasty allows for a prompt treatment of glottic insufficiency.

Collagen injection laryngoplasty is an effective and reliable method of augmenting glottic closure in patients with vocal fold insufficiency.[1-12] Multiple indications exist for this procedure; those most often cited include vocal fold paresis and paralysis, scarring of the vocal folds, vocal fold bowing, and as an adjunct to medialization thyroplasty.[1-3] Originally presented as a transoral injection performed via direct laryngoscopy under general anesthesia, the injection technique has evolved and is now typically performed as an in-office procedure.

The safety of collagen injection laryngoplasty was first addressed by Ford and Bless.[3] In their report of 45 patients treated with crosslinked bovine collagen, no major complications or hypersensitivities occurred. Although few contraindications exist for collagen injection, there is some controversy over whether it is safe to perform vocal fold injections in patients taking anticoagulants. In addition, many otolaryngologists believe skin testing for hypersensitivity reaction is necessary before collagen injection laryngoplasty. These are valid concerns that have not been adequately addressed in the literature.

Our approach to collagen injection laryngoplasty has evolved over the years. We have almost exclusively used Zyplast collagen (Inamed Corporation, Santa Barbara, California), which is bovine dermal collagen that is highly purified and lightly crosslinked with glutaraldehyde. This crosslinked bovine dermal collagen has better stability, lower immunogenicity, and longer duration than non-crosslinked collagen, and in our experience, it provides predictable results. Prior to 1999, we asked patients taking warfarin to stop taking it 5 days before the percutaneous collagen injection. In addition, we verified their anticoagulation status via laboratory blood draw by measuring the international normalized ratio (INR) on the morning of their injection laryngoplasty. On occasion, we cautiously injected

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patients if they could not safely stop taking warfarin. When no bleeding complications were observed in these patients, we stopped checking the INR values in patients taking warfarin before injection.

Hypersensitivity testing is recommended before bovine collagen injection laryngoplasty because of reactivity that has been reported in 3 percent of the population.[13] However, skin testing is performed using noncrosslinked collagen even if injection laryngoplasty is performed with crosslinked collagen. Moreover, development of autoimmune collagen vascular diseases have been postulated by several studies that examined the relations between noncrosslinked bovine collagen injections and incidence of dermatomyositis and polymyositis.[13] However, except for a few case reports involving superficial collagen deposition in the vocal folds, there are no reports of any hypersensitivity reaction or development of autoimmune disease from collagen injection laryngoplasty.[7,10,13] When we began using bovine crosslinked collagen, we routinely performed skin tests before collagen injections. We stopped skin testing when our clinical experience showed lack of hypersensitivity reactions after bovine crosslinked collagen injections.

The aim of this report is to review our experience with bovine crosslinked collagen laryngoplasty. We specifically focus on our experience injecting patients who are taking the anticoagulant coumadin and on performing injections without skin hypersensitivity testing.

METHODS

This retrospective study was approved by the IRB of the University of California, Los Angeles. Medical records of patients who were treated at the Division of Head and Neck Surgery dating from April 1997 to February 2006 were examined. Patient demographics, reason for collagen injection, anticoagulation status, and whether skin hypersensitivity was performed were noted.

All injections were performed by the senior authors (G.S.B. and D.K.C.). An informed consent, including disclosure of the remote possibility of airway obstruction and bleeding into the vocal fold, is obtained for all patients undergoing collagen injection. The nasal cavities are decongested with phenylephrine hydrochloride and anesthetized with 4 percent lidocaine. While the injection is performed, the larynx is visualized on the video monitor via a transnasal flexible laryngoscope connected to a videocamera. The surgeon palpates the external neck landmarks, including the cricoid cartilage, the cricothyroid membrane, the superior notch of the thyroid cartilage, and the hyoid bone, to assess the position of the vocal folds in relationship to these external landmarks. A 27-gauge needle is attached to the preloaded collagen syringe and then passed through either the thyroid ala or cricothyroid membrane into the paraglottic space. The collagen is injected into the muscular or the paraglottic compartment and *not* into the lamina propria layer of the vocal fold. Each vocal fold is injected until complete vocal fold closure is achieved and then slightly overinjected to account for postinjection absorption of the carrier material.

Patients can be discharged immediately following the collagen injection. When we first started in-office collagen injections, all patients returned to the clinic after 1 week for laryngoscopy. For the past decade, however, patients called or returned to the clinic only if the collagen injection did not result in improved phonation or worsened their voice. Additionally, patients were requested to report any complications such as neck hematoma, hemoptysis, shortness of breath, or any other adverse event. Patients were instructed to return to clinic in 2-3 months or when they thought that their voice was deteriorating again, for repeat collagen injection.

Although not the primary goal of this report, we also noted from the chart review if the injection was a success or a failure. Assessment of success or failure of collagen injection was made at the follow-up visits by the physician. At the follow-up visit, each patient was questioned regarding the effectiveness and duration of the collagen injection. Successful percutaneous collagen injection was defined as patient-reported subjective improvement in voice, as well as closure of the glottic gap for patients with glottic insufficiency by laryngovideostroboscopy. Failure was defined as no improvement in patient's voice or the occurrence of complications such as neck pain or bleeding. For patients on warfarin, INR values were obtained from our electronic medical record. Laboratory values within 1 month of the date of injection were considered satisfactory.

RESULTS

During the study period, 895 patients received 1290 collagen injections (Tables 1 and 2). There were 542 men and 353 women, with an average age of 68 years. The most

Table 1
Number of patients receiving collagen injection laryngoplasty by indication

Indication for Injection Laryngoplasty	No. of Patients	No. of Patients on Warfarin
Left vocal fold paralysis	331	31
Presbylaryngeus/glottic gap/ glottic insufficiency	191	7
Right vocal fold paralysis	175	7
Vocal fold bowing	116	9
Parkinson's hypophonia	60	1
Bilateral vocal fold paralysis	10	0
Dysphonia	4	2
Miscellaneous	8	2
Total	895	59

Table 2
Number of collagen injections by indication

Indication for injection laryngoplasty	One injection	Two injections	Three or more injections
Left vocal fold paralysis	257	55	19
Presbylaryngeus/glottic gap/glottic insufficiency	149	20	22
Right vocal fold paralysis	137	31	7
Vocal fold bowing	78	16	22
Parkinson's hypophonia	44	9	7
Bilateral vocal fold paralysis	8	1	1
Dysphonia	4	0	0
Miscellaneous	5	3	0
Total	682	135	78

common indication for injection laryngoplasty was vocal fold paralysis. Three hundred thirty-one patients (37%) had left vocal fold paralysis, and 175 patients (20%) had right vocal fold paralysis. One hundred ninety-one patients (21%) had presbylarynx, and another 116 (13%) had vocal fold bowing unrelated to aging. Other indications included Parkinson's hypophonia (6.7%) and miscellaneous dysphonia (0.9%).

Fifty-nine patients (7.7%) were taking warfarin at the time of collagen injection laryngoplasty. Left vocal fold paralysis constituted the largest group of patients on warfarin (31 patients), thus supporting the notion that left vocal fold paralysis is often a complication resulting from cardiac surgical procedures that subsequently require anticoagulation therapy. A total of 81 injections were performed in the patients taking warfarin. Only in 29 patients could we retrospectively locate an INR value that was performed within 1 month of the injection laryngoplasty. The range of INR values was 1.1-6.3, with an average INR of 2.3. The supratherapeutic INR level was not known to the surgeon performing the injection at that time, and there were no bleeding complications. The INR values for the other patients could not be located retrospectively either because they were obtained many years prior at various outside facilities where records were not available or because the INR values were more than a month apart from the injection date. In the majority of patients, INR values were also not recorded in the chart because we did not require it for the procedure, although all patients were taking therapeutic doses of warfarin by clinical history. No bleeding complications were recorded from the percutaneous injection laryngoplasty, including in the sole patient with an INR of 6.3. Although we do not require that INR values be obtained before injection, we recommend that if the surgeon is aware of a supratherapeutic INR level, the procedure be postponed until the INR value has returned to the therapeutic range.

Fifty of the 895 patients underwent skin hypersensitivity testing before injection laryngoplasty. None of these patients was found to develop a skin sensitivity reaction. The 845 patients who did not undergo skin testing also reported no immediate or delayed immunological reaction. There were no incidents of neck swelling, unexplained inflammation of the larynx, arthralgias, arthritis, fever, urticaria, generalized swelling, shortness of breath, or other airway complications.

Of the 1290 injections, 200 had no subjective improvement of their voice, nine reported worse voice, two reported neck pain without breathing difficulty, one could not be injected in the clinic due to difficult anatomy, and one patient had temporary loss of voice. Thus, 1077 injections (83%) were successful in improving dysphonia without complications and 213 injections (17%) reported no improvement.

DISCUSSION

Zyplast collagen has been used as an implant for injection since the late 1980s. This collagen formulation, consisting of purified bovine dermal collagen crosslinked with glutaraldehyde, has better stability and also reduces the hypersensitivity rate to less than 1 percent.[10] Prior to bovine collagen, substances used for injection laryngoplasty included Teflon, gelatin powder, fat, fascia, and autologous collagen. However, due to the viscosity of these substances, a large-bore needle system was usually necessary, and injections were made under general anesthesia via direct laryngoscopy. Additionally, more preparation was necessary to harvest the substances and more side effects were expected. The first generation of bovine collagen was not crosslinked and thus was absorbed much faster and also had a higher potential to be immunoreactive. With crosslinked bovine collagen being readily available, and having lower immunogenicity, longer duration, and lower morbidity, it became the optimal injectable for percutaneous injection laryngoplasty. New materials have been recently introduced or used off-label for injection laryngoplasty, including hydroxylapatite, hyaluronic acid, and micronized collagen. However, we have continued to prefer Zyplast collagen because we believe its viscosity and material/syringe/needle system provides superior operator feedback for in-office vocal fold injection and provides predictable results, compared with other materials and injection systems.

Percutaneous collagen injection has been used to treat a variety of vocal fold pathologies, including scarring, atrophy, and glottic gaps.[14] Although there are reports of some benefit of collagen injection for patients with vocal fold scarring,[6] our experience in vocal fold scarring have not been the same. This is because the viscoelasticity of collagen does not mach the vocal fold lamina propria layer. Currently, no vocal fold injection material exists that matches the viscoelastic properties of the vocal fold lamina propria layer and also provides long-term success in treating loss of this layer.

Warfarin interferes with blood coagulation by impairing the hepatic synthesis of vitamin K-dependent clotting factors and, more specifically, factors II, VII, IX, and X. Patients with certain medical conditions, such as venous thromboembolism, post-myocardial infarction status, atrial fibrillation, and mechanical heart valves, are routinely placed on warfarin therapy due to its efficacy and cost.[12] Oftentimes, patients have vocal fold paralysis as a result of cardiac procedures necessitating life-long anticoagulation. Elderly patients with presbylarynx often have other concurrent cardiovascular illnesses that require warfarin anticoagulation as well. It is reasonable to expect that a significant proportion of our clinic population will include patients taking warfarin. For these reasons, we must consider the safety of percutaneous injection in this subset of patients.

Vocal fold hematomas in patients on anticoagulation have been described in the literature previously. Kerr and Kwaselow[15] described two cases of vocal fold hematomas that occurred spontaneously in patients taking warfarin. Both patients presented with hoarseness and cough, and one patient required intubation to secure his airway. However, these patients did not have vocal procedures as the cause of their hematomas. Neely and Rosen[16] describe vocal fold hemorrhage in an opera singer. The 59-year-old patient was taking warfarin due to his personal history of atrial fibrillation. The patient underwent excision of a vocal fold polyp and carbon dioxide laser ablation of vascular ectasia feeding the vocal fold polyp. The patient discontinued the warfarin for 3 weeks before the procedure. However, he later developed recurrent dysphonia following aggressive singing, and videostroboscopy confirmed the hemorrhage of the left vocal cord.

In anticoagulated patients with glottic insufficiency, otolaryngologists have to confront the dilemma of when is the optimal time to perform injection laryngoplasty. The benefits of collagen injections have to be weighed against the potential dangers of discontinuing anticoagulants. By using the percutaneous method for injection laryngoplasty, our experience shows that patients can safely receive the immediate benefits of collagen injections without bleeding complications. It is important to note that we exclusively use a 27-gauge needle, and use of a larger needle for injection laryngoplasty is expected to lead to increased risk of bleeding complications.

Few other complications from percutaneous laryngoplasty have been reported. Zapanta and Bielamowicz[17] described the case of a 54-year-old woman who developed a small laryngeal abscess following injection with micronized collagen (Cymetra; LifeCell Corporation, Branchburg, NJ). She presented with throat pain, shortness of breath, and voicing problems 4 days after transoral injection of Cymetra into the lateral aspect of her thyroarytenoid muscle. A computed tomography scan subsequently revealed a 1.3 $\times$ 0.4-cm abscess in her left hemilarynx, which resolved with oral steroids and antibiotics. Sataloff and Anderson[13] reported submucosal firm deposits that required surgical removal following collagen injection into the lamina propria of the vocal folds.

Due to the lack of hypersensitivity reactions after bovine crosslinked collagen injections to the larynx, we have also discontinued performing preinjection skin testing. Review of the literature shows only one case of a reported hypersensitivity reaction in the larynx with noncrosslinked bovine collagen, with the patient experiencing erythema at the injection site 1 week after treatment.[5] All other positive skin hypersensitivity reports were in cases of collagen injections for facial rejuvenation.

Our study data are imperfect; patients did not have routine early follow-up, for example, within 1 week postinjection, specifically looking for bleeding and hypersensitivity complications. Moreover, we relied on patients' self-reporting to document complications that may have occurred after patients were discharged from the clinic. Thus, it is possible that some of our patients on warfarin may have developed minor bleeding or other subtle vocal fold changes and may not have recognized them or reported them. No patients on anticoagulation, however, reported any worsening of hoarseness. Specifically, there was no report of neck hematoma, hemoptysis, or evidence of a major bleeding at follow-up laryngoscopy several months later. Furthermore, it could be reliably concluded that those who reported successful injection most likely had no complications. This group comprised 83 percent of the injections. Our criterion of success is the subjective impression of the patient, but this is often the best criterion for success in clinical practice.

In this review, we retrospectively assessed bleeding complications in patients taking warfarin who underwent injection laryngoplasty using a 27-gauge needle and the safety of performing bovine crosslinked collagen injection laryngoplasty without prior hypersensitivity skin testing. Our experience shows that it is safe to perform percutaneous collagen injection laryngoplasty in patients taking warfarin. Thus, cessation of anticoagulation is not necessary, especially if it poses a significant risk to the patient. We also find that it is safe to perform collagen injection laryngoplasty with bovine crosslinked collagen without prior hypersensitivity testing. We see practicality in our approach to collagen injection laryngoplasty. Patients on warfarin do not have to incur the cardiovascular risk and the delay in obtaining a therapeutic injection from stopping the medication. Patients with dys-

phonia and dysphagia do not have to wait several weeks before receiving their injection as the skin testing is performed and results determined, and instead they can obtain immediate benefits of the improvement in phonation and reduction in the risk of aspiration.

CONCLUSION

We find that percutaneous collagen injection laryngoplasty using a 27-gauge needle is safe in patients taking warfarin. However, the decision to perform such injections in anticoagulated patients rests with the physician performing this procedure and his or her comfort level with the potentially increased risk. Also, in our experience, prior skin hypersensitivity testing is unnecessary, as no serious allergic reactions have occurred in our practice. This applies specifically to percutaneous bovine crosslinked collagen, as it has been almost exclusively our injection material of choice.

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