Collagenase Followed by Compression for the Treatment of Earlobe Keloids

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BACKGROUND  Many therapeutic options are available for treating keloids, but success rates vary widely, and the keloids often recur. The Food and Drug Administration has recently approved intralesional collagenase for the treatment of Dupuytren’s contracture. This medication has not been explored for the treatment of earlobe keloids, a common problem.

OBJECTIVE  To evaluate the safety and clinical efficacy of intralesional collagenase followed by compression for the treatment of earlobe keloids.

MATERIALS AND METHODS  Six earlobe keloids in six patients were injected with a commercial collagenase preparation. Study participants were asked to use compression earrings daily thereafter. Patients were examined and photographed 1 day, 2 weeks, 4 weeks, 10 months, and 12 months after injection. Adverse events were assessed at each visit, and the keloids were measured and photographed.

RESULTS  All patients had a decrease in the size of their earlobe keloid by an average of 50% ($p = .02$). Three of the six participants chose to have their earlobe keloids surgically excised for cosmetic reasons 6, 8, and 11 months after enrollment, so measurements for data analysis for these patients were taken after only 1, 1 and 10 months. All participants returned for follow-up at the last study visit 1 year after study commencement. The three patients who completed the study were pleased with the improvement of their earlobe keloid, although complete clearance was not achieved. Side effects included injection site swelling, tenderness, and one ulceration that spontaneously resolved within 2 weeks.

CONCLUSION  Intralesional collagenase followed by compression appears to be a safe and modestly effective treatment for earlobe keloids. This approach warrants further investigation in larger studies with longer follow-up in motivated patients who decline surgical excision.

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Keloids and hypertrophic scars are common problems, especially in people of African, Hispanic, and Asian descent.1 Clinically, keloids extend beyond the original wound and can have a deep red or purple color. Keloids are characterized histologically by disorganized, thick, hyalinized collagen with a prominent mucoid matrix.2 The pathogenesis of keloids has not been fully elucidated, but the primary biochemical feature is an imbalance of matrix degradation and collagen biosynthesis, resulting in excess accumulation of collagen in the wound.3 Oddly, levels of collagenases have been found to be three to four times as high and 14 times as active as in normal scars.4,5 In addition, a defect in apoptosis and abnormal expression of many growth factors, enzymes, and interleukins

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have been postulated to play a role in the formation of a keloid.6

A variety of methods have been used to treat keloids, including intralesional steroids, imiquimod, 5-fluorouracil, and interferon alpha, as well as procedures involving lasers, surgery, radiation, cryotherapy, and silicone gel sheeting and combinations of these treatments.2,7,8 However, there are many limitations, including long treatment duration, poor efficacy, recurrence, and side effects.2,7,8 Although radiation therapy has been reported to be effective, the risk of later malignancy is a deterrent.9 Furthermore, well-designed randomized clinical trials with large patient populations and long-term follow-up are lacking.

Compression has been used as monotherapy as well as in combination therapy for the treatment of earlobe keloids. The Food and Drug Administration (FDA) has not approved compression devices, which are Class I medical devices that plastic surgeons commonly dispense after surgical excision of earlobe keloids or as an adjunctive treatment after intralesional steroid treatment, for keloid compression. Russell and colleagues10 treated 30 patients with earlobe keloids using a Zimmer splintage (compression device) alone over 10 years and found a 50% or greater reduction in the size of the keloids at 1 year. Other investigators have used compression devices in combination with other treatment modalities. For example, Hassel and colleagues11 surgically excised earlobe keloids and then asked their patients to wear a compression acrylic device for at least 23 hours a day. They found that two of the 10 patients experienced a recurrence noted at a follow-up visit at 18.2 months and concluded that the wearing time of the compression splint for at least 10 hours a day appeared critical for the success of the treatment. They also discovered that the need for additional intralesional steroid injections was significantly lower in patients wearing the splint for more than 20 hours per day. Eight patients reported that the splint treatment was painless and were happy with the therapeutic result.

Recently, the FDA has approved collagenase (Xiaflex; Auxilium Pharmaceuticals, Malvern, PA) for the treatment of Dupuytren’s contracture, which shares with keloids the presence of thickened collagen bundles. Collagens are predominant proteins in the connective tissue of humans and animals. Dupuytren’s contracture is caused by excessive pathologic collagen production and deposition in palmar tendons, limiting hand function.12 In a double-blinded placebo-controlled randomized prospective trial, collagenase was injected into the affected palmar tendons of 22 patients, and after 24 hours the treated tendons were manipulated to attempt ruptures.12 The authors reported statistically significant improvement of contracture (64% with collagenase vs 6.8% with placebo). Because keloids and Dupuytren’s contracture share a common final pathway, we hypothesized that collagenase (Xiaflex) with the help of subsequent compression might improve keloid scars on the earlobes. Furthermore, the same approach might prevent or improve keloid scars on other areas of the body. Of note, however, Kang and colleagues13 examined laboratory-grade collagenase (Sigma Chemicals, St. Louis, MO) in seven patients with hypertrophic scars and keloids, albeit without subsequent compression. They noted a 33% reduction in scar volume, but this reduction was not sustained beyond 6 months even with up to five repeat injections of collagenase.

We now report the results of a pilot study designed to investigate the effects of a single intralesional injection of commercially available FDA-approved collagenase followed by compression for the treatment of earlobe keloids.

Methods and Materials

Boston University and Boston Medical Center Institutional Review Board approval and an investigational new drug application was obtained from the FDA. All patients gave informed consent.

Six patients were enrolled (5 female, 1 male, aged 20–42). Pregnant women were excluded from the
study. All patients had a 1-year or longer history of earlobe keloid at least 5 mm in largest diameter. The earlobe keloid enrolled for the study in all patients had previously been excised more than 1 year before and had subsequently recurred.

The Investigational Drug Service of the Boston Medical Center Pharmacy Department reconstituted collagenase clostridium histolyticum (0.45 mg, less than the 0.58 mg approved for the injection of Dupuytren’s contracture12) using the 0.9-mg powder vial reconstituted in sterile diluent (0.39 mL) that the manufacturer provided. Using a 30-G needle, 0.195 mL was injected directly into the center of the affected keloid at baseline. The high cost of the collagenase preparation precluded repeat injections in this investigator-initiated protocol.

All participants were given a pair of acrylic compression earrings (Delasco, Council Bluffs, IA) and asked to apply one to the treated earlobe keloid at least 8 hours per day until the end of their participation at 12 months. At each follow-up, the investigator collected study diaries in which subjects were asked to record the number of hours the compression earrings were worn per day; assessed subjects for adverse events; measured keloid height, length, and width using digital calipers, and took photographs. Tissue samples of the treated keloid were obtained in the three subjects who chose to undergo keloid excision during the study. No participants dropped out of the study otherwise, and all returned for their last study visit.

Results

During the first month, all patients kept a daily written record of hours they wore the compression earrings, recorded as 6 to 8 hours, average 7 hours per day. Written logs were not kept for months 2 to 12, but patients recalled less usage.

No serious local side effects were experienced. All participants reported postinjection earlobe keloid tenderness and swelling that resolved within 1 week. Caliper measurements on day 1 revealed an average 91% increase in keloid volume. One patient had blistering of the injected site followed by ulceration that healed within 2 weeks of daily emollient application.

Keloid volume decreased maximally from baseline by 33% to 91% (average 67%; Table 1), and in two of the six patients, this maximal reduction was present at 12 months, the study’s conclusion (Table 2). Because of recurrence in one keloid, average reduction at 12 months was 50%. In three of the patients, maximal reduction was observed at 1 month, although in two of these patients, no further measurements were possible because the keloids were excised before the next study visit. The patient with the largest reduction in keloid size (91% at 12 months) was not seen after 2 weeks, when there was already a 37% reduction, until the final measurement. In the five of six patients seen at 2 weeks, all had a reduction in keloid size that averaged 34% from baseline (Table 2). One patient had maximal improvement at 10 months, with marked reoccurrence of the keloid between 10 and 12 months. In the only other patient seen at the 1-, 10-, and 12-month visits, there was progressive reduction in keloid size. At the last study visit, average reductions were statistically significant. All patients achieved a reduction in keloid size that averaged 43% at the last measurement month in those who had their keloid excised and 56% at 12 months in those who completed the study (Table 2). All treated earlobe keloids were observed to be softer at subsequent follow-up visits (Figure 1). The three participants who initially complained of pruritus were asymptomatic at all follow-up visits.

One patient with bilateral keloids had both excised 8 months after collagenase injection of one. There were no differences between the treated and non-treated sites in appearance of the collagen fibers (Figure 2). The other two excised keloids could not be compared with untreated lesions but were typical in appearance (data not shown).
The incidence of keloids has been reported to be as high as 16% of patients after piercing or surgical procedures, mostly in patients with darker skin color. The disfiguring appearance of keloids may affect patients of all skin types, whether they occur spontaneously, related to syndromes such as Rubinstein-Taybi and Goeminne, or as a result of trauma from surgery, piercings, accidents, infections, or other inflammatory processes. In addition to being a cosmetic problem, keloids may be pruritic or painful and interfere with function.

In Nigeria, where keloids are common, 47 (35.9%) interviewed patients reported that they limited social
interaction. Sixteen (12.2%) patients reported that keloids affected their work, of whom four (25.0%) described this happening when keloids became infected. Twelve (75.0%) stopped work because they felt psychologically troubled by keloids. In Germany, where the incidence of keloid formation is lower and thus lesions are presumably less acceptable, Bermeuller and colleagues reported significant psychological distress in their patients with earlobe keloids because of their high visibility and difficulty in disguising the lesion.

In this study, we found that collagenase injections in combination with compression earrings resulted in a significant overall 66% maximum reduction in size of the keloids. Reduction in size was maximal after the first month in the two patients who had their keloids excised before the next scheduled measurement at 10 months; after 10 months in the two patients seen at each scheduled study visit with slight and marked recurrence by 12 months, respectively; and 12 months after injection in the other two patients. The results are especially promising in these patients, all of whom had a history of keloid recurrence after excision. As expected, because of the novelty of this new treatment, participants in our study were fairly adherent with the compression earrings, especially during the first month of the study, as recorded in study diary and reported by the subjects. These data suggest that compression with pressure earrings may help mechanically degrade the excess accumulation of collagen, although a formal noncompression comparison was not possible within the study design. Whether greater improvement would have resulted from greater use of the compression earrings is unknown.

Reoccurrence of keloids after any type of therapy is a major problem and often occurs after a delay of a year or longer. In our small study, only three patients could be evaluated after 12 months, and two of these had keloid regrowth between 10 and 12 months, although only one keloid was larger than at baseline. Thus, we observed a sustained decrease in size of the keloids at 1 year follow-up after a single collagenase injection in two of the three evaluable patients. In contrast, Kang and colleagues found regrowth of the keloid to the baseline size or greater within 6 months in all patients using a different collagenase preparation, without subsequent compression.
The collagenase injection was well tolerated; the most common side effect was injection site tenderness, which resolved within a week.

The small study population and lack of compression-only and injection-only control groups limit interpretation of this pilot study. Regardless, it demonstrated that intrallesional collagenase followed by compression with pressure earrings is a treatment option for earlobe keloids, especially in patients who are not interested in surgery.

Conclusion

New approaches for preventing keloids and hypertrophic scars are being explored, but patients who have already developed these disfiguring lesions are limited by the available treatments. A single collagenase injection followed by compression demonstrated significant and sustained decrease in earlobe keloid size over a 1-year period and deserves further study.

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