Medical and surgical therapies for keloids

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ABSTRACT: Keloids are benign, but sometimes painful and/or pruritic, proliferative growths of dermal collagen, usually resulting from excessive tissue response to trauma. Although benign, the social and psychological impact on affected individuals must be considered. Keloids often arise secondary to ear piercing and operative procedures. No single treatment modality is always successful. The more common ones are discussed. Some of the medical therapies include corticosteroids, interferon, 5-fluorouracil, and imiquimod. Primary excision and cryosurgery are among the major surgical options. Radiation therapies and other physical modalities are also discussed.

KEYWORDS: corticosteroids, excision, 5-fluorouracil, imiquimod, interferon, keloids

Keloids are benign hyperproliferative growths of dermal collagen that usually result from excessive tissue response to skin trauma FIGS 1–4. There are, however, spontaneous keloids which arise without a history of trauma to the involved site. Keloids are often pruritic and/or painful, and although benign, they invade clinically normal adjacent skin.

Because of ear piercing, younger females have a higher incidence of keloids than males. People over 65 years of age seldom develop keloids; however, because of increased mid-chest operative procedures and coronary artery bypass surgery, there has been an increase in the incidence of sternal keloids in the elderly FIG. 5.

Keloid therapy is fraught with varying degrees of success. There is no one modality that is always successful. Many anecdotal reports of therapeutic success have proven untrue when investigated in randomized clinical trials. Also, there is no animal model that can be used for clinical investigation. The more common medical, surgical, radiation, and physical modalities used to treat keloids will be discussed in the present paper.

Prevention should be the first rule of keloid therapy. Nonessential cosmetic surgery should not be performed on known keloid formers (those patients

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FIG. 1. Large keloid on a patient's left anterior earlobe.

FIG. 2. Linear keloid on a patient's right lateral neck.

FIG. 3. A crab-like keloid on the mid-chest area of a patient.

FIG. 4. Three keloids of different sizes and shapes on a patient's right anterior arm.

with only earlobe keloids should not be considered keloid formers); mid-chest incisions should be avoided whenever possible; all postoperative and cutaneous trauma sites should be treated with appropriate antibiotics to prevent infection; all surgical wounds should be closed with normal tension; if possible, incisions should not cross joint spaces and skin excisions should be horizontal ellipses in the same direction as the skin tension lines.

Medical therapies

Steroid injections

One of the long-term standards of keloid therapy, and the most commonly used therapeutic modality, is the injection of triamcinolone acetonide (10–40 mg/mL). The patients should be told in advance that the injected areas might become hypopigmented and that these areas may remain that way for six to twelve months. Since the triamcinolone

injections can be quite painful, EMLA or L-M-Y-, previously known as ELA-Max, should be used one to two hours prior to injecting. Also, injecting lidocaine with epinephrine around the lesions prior to using intralesional (IL) triamcinolone will greatly reduce the pain of injection and allow the patient to tolerate multiple needle pricks. After each injection, the syringe should be tested to see if the needle is clogged. Because of the hardness of the keloid tissue, needle insertion may act as a needle biopsy. The needle should be inserted and triamcinolone injected in the papillary dermis, where collagenase is produced. The injected steroid should not be put into subcutaneous tissue, because this may cause underlying fat atrophy. Precipitation of the steroid carrier may appear as yellowish lumps below the atrophic injection site. The corticosteroid inhibits alpha$_2$-macroglobulin which, in turn, inhibits collagenase. Once this pathway is blocked, collagenase is elaborated, thus enabling collagen degeneration (1). Keloid injections can be made easier and less painful if first treated with liquid

FIG. 5. Keloid secondary to a sternostomy for cardiac bypass surgery.

nitrogen for a 10–15-second thaw time. This causes cutaneous edema, thereby allowing easier injection. To prevent post-IL corticosteroid clinical rebound, the injections should be given every two to three weeks. Prior to initiating IL triamcinolone therapy, patients should be warned that they may also develop atrophy and telangiectasias at and around the injection sites.

The use of pressure or silicone gel-sheeting therapy in conjunction with IL triamcinolone is more efficacious than when either modality is used as a monotherapy.

Interferon therapy

Interferon-alpha and -gamma inhibit types I and III collagen synthesis via a reduction in cellular messenger ribonucleic acid (2). Berman and Flores (3) reported an 18.7% recurrence rate when interferon alpha-2b injections were given after keloids excision versus a 51% recurrence rate with excision alone, and a 58% recurrence rate when treated with excision and postoperative IL triamcinolone. One million units are injected into each linear centimeter of the skin surrounding the postoperative site, immediately after surgery and one to two weeks later. For large excision sites, the patients should be premedicated with acetaminophen to help negate the flu-like symptoms caused by the interferon. Interferon treatment is quite expensive for patients who undergo surgical excision for many keloids or large keloids.

5-flurouracil therapy

Intralesional 5-flurouracil (5-FU) has been used successfully to treat small isolated keloids (4). Better results are obtained when 0.1 mL of triamcinolone acetonide 10 mg/mL is added to 0.9 mL of 5-FU (50 mg/mL). This mixture is initially injected into the keloids three times per week, and the frequency is then adjusted according to the response. The average scar required five to 10 total injections, usually given weekly. The major limiting factor in using 5-FU is the pain of injection. This leads to noncompliance for many patients.

Imiquimod therapy

Imiquimod 5% cream induces local production of interferons at the site of application. Based on this information, Berman and Kaufman (5) applied imiquimod cream to the postoperative excision site of 12 patients who had a keloid removed surgically. Application of imiquimod should be started immediately after surgery and continued daily for eight weeks. Berman's patients were evaluated 24 weeks post-excision and none had recurrence of their keloids. Most patients experience mild to marked irritation secondary to the daily application of imiquimod. Those with marked irritation will sometimes have to discontinue the medication for several days to a week and then resume therapy. Patients who have large surgical sites and wounds closed with flaps, grafts or tension should not start imiquimod cream therapy for four to six weeks postoperatively, because early application often causes the surgical site to splay or dehisce. More than 50% of the patients developed hyperpigmentation of the treated site.

Other medical therapies

Flurandrenolide tape (Cordran) applied to the keloid for 12–20 hours a day will usually cause the keloid to slowly soften and become flatter. It will also

usually eliminate the accompanying pruritus. Long-term use may cause cutaneous atrophy.

For small keloids, IL injection of bleomycin (1 mg/mL, 0.1–1 mL) has been reported to cause complete regression of some lesions (6).

Clobetasol ointment or gel, applied b.i.d., may soften and/or flatten keloids in addition to eliminating the accompanying pruritus, pain and tenderness often associated with keloids. Long-term use will cause perilesional hypopigmentation, atrophy and telangielasea of the treated areas.

Tacrolimus is a new member of the keloid therapy armamentaria. Research by Kim et al. (7) found increased expression of the *gli-1* oncogene in keloids, but not in normal scar tissue. Since tacrolimus may mute the *gli-1* oncogene, it has been used as a therapeutic alternative on a b.i.d. basis. Longer and larger studies are needed to determine its effectiveness.

When combined with surgical excision, methotrexate has been reported to prevent most recurrences. Fifteen to 20 mg of methotrexate is given orally in a single dose every four days starting a week prior to surgery, and continued for three or four months after the postoperative site is healed.

Pentoxifylline (Trental) 400 mg t.i.d. has been somewhat successful in preventing recurrence of excised keloids. Its mechanism of action is not fully understood, but may be a result of improved circulation, which, in turn, sweeps away fibroblast growth factors.

Colchicine has been used to treat and prevent recurrence of keloids via inhibition of collagen synthesis, microtubular disruption, and collagenase stimulation (8).

Since topical zinc inhibits lysyl oxidase and stimulates collagenase (9), it has been used to treat keloids, but has had limited success. Topical tretinoin applied twice a day has been reported to alleviate pruritus and other keloid symptoms, and may cause various degrees or regression (10).

Other medications tried but found to have limited therapeutic success or a questioned risk–benefit ratio are IL verapamil (11), cyclosporine (12), methotrexate, D-penicillamine (13), and Relaxin (14).

Surgical therapies

Before excising a keloid the physician should be aware of the major risk factors associated with keloid recurrence:
1. a family history of keloids (especially in African Americans);
2. an infected operative site;
3. anatomic location (especially the mid-chest and shoulders);
4. type of precipitating injury (thermal or chemical burn);
5. tension of postoperative site; and
6. dark skin (Fitzpatrick 4–6).

Also, the recurrence rate for simple excision surgery of a keloid without postoperative adjunctive measures varies from 50% to 80% (15).

Primary excision

The easiest and one of the most commonly performed procedures for keloid removal is surgical excision followed by IL corticosteroid injections. Prior to excision, the operative site is anesthetized with a half-and-half mixture of 2% lidocaine with epinephrine and triamcinolone acetonide 40 mg/mL. For keloids with narrow bases (1 cm or less), a simple excision followed by undermining the base and closure with interrupted sutures is recommended. For keloids with wide bases, flaps and grafts may be required to close the postoperative site without tension. Most excised keloids need adjunctive therapy such as IL corticosteroids, pressure, silicone gel-sheeting, imiquimod cream or interferon injections. Sutures need to stay in for 10–14 days because the lidocaine steroid mixture used to anesthetize the lesion will delay wound healing.

Therapy is more complex for large, nonpedunculate earlobe keloids and keloids with wide bases on other parts of the body. First, a half-moon or tongue-like flap is made from the smoothest and flattest portion of the lesion, large enough to cover the base of the excised keloid. The tongue flap is sutured in the base of the excised keloid with 5 or 6–0 nylon sutures, which are left in for 10–14 days in order to prevent wound dehiscence. The postoperative site is injected with 10–40 mg/mL of triamcinolone acetonide Starting one week after suture removal (earlier injection, especially at the time of suture removal may cause the wound to dehisce), and repeated every three weeks × four visits to help prevent keloid recurrence. Patients should be informed that the steroid injection sites may become hypopigmented and remain so for 6 months or more. Pressure garments and silicone gel-sheeting are usually important therapeutic adjuncts. For an earlobe keloid postoperative site, special pressure earrings with a silicone backing are available. They should not be applied until two weeks after suture removal because earlier use may cause the wound to dehisce.

In cases where an autograph is not possible to close the excised lesion, a tissue expander may be inserted under the keloid and gradually expanded to enable the keloid to be excised and closed primarily, without tension.

For patients with large lesions or multiple lesions, primary excision is often not feasible. Debulking the lesion(s) by shaving to the level of the surrounding clinically normal skin, followed by eight weeks of topical imiquimod therapy, is sometimes successful. The postoperative site usually becomes hyperpigmented and does not match the texture of normal skin.

Cryosurgery

Freezing a keloid with liquid nitrogen causes cell and microvascular damage. The resulting anoxia causes tissue necrosis and sloughing, followed by tissue flattening (16). A freeze-thaw time of greater than 25 seconds will usually result in hypopigmentation secondary to melanocyte destruction, especially for people with Fitzpatrick skin types IV–VI. Two, 15–20-second thaw cycles on each visit every three weeks × 8–10 visits usually results in complete flattening in more than half of the cryo-treated patients. When cryosurgery was used in combination with IL steroids, it resulted in an 84% positive response rate (17). Many patients do not return for follow-up cryosurgery because of the postoperative pain, morbidity and slow healing. Also, the hypopigmentation may last for years. Cryofreezing may also be used to cause mild tissue edema enabling easier injection of IL steroids.

Radiation therapy

Radiation may be used as a monotherapy or combined with surgery to prevent recurrence of keloids following excision. When used as a monotherapy, radiation is not very effective (a recurrence rate of 50–100%) (18) unless large doses are used, however, this may lead to squamous cell carcinoma of the skin of the treated sites 15–30 years later. A case of medullary thyroid carcinoma has been described in an 11-year-old boy eight years after excision and postoperative radiation of a chin keloid (19). Primary radiation is also successful in alleviating the pruritus, pain and tenderness of keloids.

Radiation is more effective if given the first two weeks after excision, when fibroblasts are proliferating. The usual dose is 300 rads (3 Gy) q.o.d. × four to five days or 500 rads (5 Gy) q.o.d. × three days starting on the day of surgery. Young children with keloids should either not be irradiated, or if it is the only viable option, the metaphyses should be shielded in order to prevent retardation of bone growth. Combined preoperative and postoperative radiation has no greater efficacy than postoperative radiation alone. Irridium 192 interstitial irradiation after surgical excision had a recurrence rate of 21% in 783 keloids (20).

Since delivery of the radiation dose can be better targeted with brachytherapy than with external beam irradiation, high-dose-rate (HDR) brachytherapy was used to treat keloids post-excision (21). High-dose-rate brachytherapy was administered at a dose of 1200 Gy, delivered in four equal factions over the first 24 h after surgery. Recurrence developed in eight patients (4.7%). This included five out of 147 patients (3.4%) who underwent surgical excision followed by HDR brachytherapy, and three out of 22 patients who had been treated with HDR brachytherapy alone. Cosmetic results were good or excellent in 88–94% of patients treated with excision plus HDR brachytherapy. All patients responded to HDR brachytherapy with a reduction in pruritus, redness, or burning. Thus, HDR brachytherpay combined with surgical excision seems to safely and effectively treat keloid scars and prevents their recurrence.

Physical modalities

Pressure

Pressure gradient garments (Jobst) are an adjunct for treating keloids postoperatively to prevent recurrence and are used to treat keloids after applying a potent topical steroid or flurandrenolide tape. The latter method enables reduction in the size and thickness of keloids by decreasing IL mast cells (which are increased in keloids) and decreasing histamine production which is also increased in keloids. Pressure seems to decrease alpha-macroglobulins, which inhibit collagenase breakdown of collagen. Other possible mechanisms of pressure therapy are a decrease in scar hydration, resulting in mast cell stabilization and a decrease in neovasculaization and extracellular matrix production (22), or marked hypoxia, which leads to fibroblast and collagen degeneration.

Other methods to apply pressure to keloids are ace bandages, elastic adhesive bandages, compressions wraps (Coban), pressure earrings, and tubular support bandages.

Since pressure therapy is a long-term treatment, patient compliance decreases as the duration of therapy increases.

Ligatures

Ligatures may be used for pedunculated keloids in situations where surgery is either contraindicated or refused by the patient. A 4–0 nonabsorbable suture is tied tightly around the base of the keloid and a new one is applied every few weeks. The sutures gradually cut into and strangulate the keloid, causing it to fall off. Sometimes the patient requires a few days of pain medication (Acetaminophen) after the ligature is applied. Pressure garments have a life span of only several months, and therefore, for maximum effect ,they should be replaced before they wear out.

Lasers

The use of lasers to treat keloids has had mixed results. The argon laser was the first used for keloid therapy. It seemed to only be successful in early keloids which were undergoing vascular proliferation; however, more recent studies failed to show any improvement of the keloids treated with the argon laser except an improvement in pruritus and other symptoms over several months.

The carbon dioxide laser, when used as monotherapy, has a 40–90% recurrence rate which, even if combined with postoperative IL corticosteroids, still has high recurrence rates. Its major use today is to debulk large keloids so they can be treated with other modalities.

The neodymium:yttrium-aluminum-garnet (Nd:YAG) 1064-nm laser seems to affect collagen metabolism; it was selectively inhibited without affecting fibroblast viability or DNA replication (23). A three-year follow-up of two of these patients revealed softening, size reduction and normalization of color, but because of such a small patient sample, these results cannot be extrapolated to a large population of keloid patients. Another study (24) reported improvement of keloids in 16 of 17 patients treated with the Nd:YAG laser. Unfortunately, no significant follow-up was discussed.

The 585-nm pulsed-dye laser has been used to successfully treat sternostomy scars (25). There was a significant decrease in scar height, pruritus and erythema in most of the laser treated patients. The results persisted for at least 6 months. Combining IL triamcinolone with the pulse-dye laser increased the effectiveness of keloid therapy.

Silicone gel-sheeting

Silicone gel-sheeting is a soft, gel-like covering used to treat keloids. Its mechanism of action appears to be a combination of hydration and occlusion. In addition, TGF beta-2 may be downregulated when exposed to silicone. Nonsilicone gel dressings have showed similar success. The younger the keloid and the patient, the better the response. Children like it because the gel-sheeting is painless. It usually takes 6–12 months of therapy to achieve the best results, but most patients become noncompliant after several months of therapy because of its duration, and the inconvenience of cutting and placing the silicone gel-sheeting on the keloid. To prevent maceration and secondary infection of the covered skin, the gel-sheeting should be worn 22–23 hours a day, and removed once daily for cleaning the site and making sure that air gets to the covered site.

Most of the sheets last 2–3 weeks and then start degenerating. The gel itself does not seem to be as effective as the gel-sheeting.

Polyurethane dressing (Curad) 20–22 hours a day softens keloids and causes some regression after 8 weeks of therapy. The success is increased three to four times if polyurethane is used with compression.

New potential therapies

Some of the new potential therapies are:
1. Long-wavelength ultraviolet A (340–400 nm; UVA1) may help prevent keloid recurrence after excision via its ability to decrease mast cells.
2. Quercetin, a flavonol, has been found to inhibit proliferation and contraction of excessive scar-derived fibroblasts.
3. Prostaglandin E_2 (Dinoprostone) seems to restore normal wound repair.
4. A strong bleaching agent since keloids have not been found in albinos and have regressed when vitiligo develops in the skin overlying the keloid.
5. A potent mast cell inhibitor since mast cells are not only increased in keloids, but also have an intimate relationship with fibroblasts in the inflammatory and stable border of the keloid. The contral regressing area of the keloid has no fibroblast-mast cell intimacy.
6. Gene therapy.

Summary

Keloids are medically benign, but often psychologically and socially malignant, lesions secondary

to an abnormal connective tissue response in predisposed individuals. They pose a tremendous challenge to the treating physician because of their high rate of recurrence and lack of response to therapy. Although the current gold standard of care is excision followed by postoperative IL steroid injections or use of other adjuvants, the myriad of therapeutic alternatives illustrates that there is still no single therapy that is 100% effective. Thus, there is need for continued research on keloid therapy.

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