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Why don't we have more Effective Treatment for Keloids?

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SUMMARY Numerous treatment modalities have been used to treat keloids and hypertrophic scars, but optimal treatment has not yet been established. The failure of achieving better therapeutic results in treating keloids highlights the essential problem that the pathogenetic mechanisms causing keloids remain unclear. Increased understanding at the molecular level will lead to the development of new therapies. Prevention is the first rule in keloid therapy. Conventional and experimental therapeutic approaches are presented in this review but further investigation is needed in relation to safety, adverse effects, and therapeutic efficacy. Because of the high recurrence rate of keloid scars, a follow-up period of at least 1 year is required to enable the start of treatment of recurrences as expediently as possible and to evaluate long-term success.

KEY WORDS: keloids, intralesional corticosteroids, excision, radiotherapy, laser, cryosurgery

INTRODUCTION

Keloids are benign, well-demarcated areas of fibrous tissue overgrowth that usually develop at the site of injury or surgical wound. The first description of abnormal scar formation in the form of keloids was recorded in the Smith papyrus regarding surgical techniques in Egypt around 1700 BC (1). Baron Jean-Louis Alibert (1768-1837) identified keloid as an entity in 1806. Alibert used the term cheloide, derived from the Greek *chele*, or crab's claw, to describe lateral growth of tissue into the unaffected skin (2).

The difference between keloid and hypertrophic scar was for the first time described by Mancini in 1962 and confirmed by Peacock in 1970 (3). A hypertrophic scar looks similar to a keloid and it is more common. Hypertrophic scars are raised, erythematous, pruritic, fibrous lesions that typically remain within the confines of the original wound, usually undergo at least partial spontaneous resolution over widely varying time courses, and are often associated with contractures of healing tissues (4). Keloids, by contrast, may start some time after the injury and extend beyond the wound site. This tendency to migrate into surrounding areas that were not injured distinguishes keloids from hypertrophic scars. Keloids typically appear

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following surgery or injury, but they can also appear spontaneously or as the result of some mild inflammation, such as an acne pimple on the chest (even if not scratched or otherwise irritated).

Keloids and hypertrophic scars represent aberrations in the fundamental processes of wound healing, which include cell migration and proliferation, inflammation, increased synthesis and secretion of cytokines and extracellular matrix (ECM) proteins, and remodeling of the newly synthesized matrix (5).

EPIDEMIOLOGY AND ETIOLOGY

Keloids are only found in humans and occur in 5%-15% of wounds (2,6). They tend to affect both sexes equally, although a higher incidence of women presenting with keloids has been recorded, possibly secondary to cosmetic implications associated with disfigurement (7). There is a familial tendency towards keloids. The frequency of keloid occurrence in persons with highly pigmented skin is 15 times higher than in persons with less pigmented skin (8). In a random sample of black individuals, as many as 16% reported developing keloid scars, with an incidence rate of 4.5%-16% in the black and Hispanic populations (8). In some tribes in Africa, keloids are an integral part of ritual scarification. Most reported cases of keloids have occurred in patients between the ages of 10 and 30 years. The incidence of keloids is also increased in patients with other connective tissue abnormalities such as Ehlers-Danlos syndrome and systemic sclerosis (9).

PATHOGENESIS

The pathogenetic mechanisms that cause keloids are still unclear. The most important risk factor for the development of abnormal scars such as keloids is wound healing by secondary intention, especially if healing time is greater than 3 weeks. Wounds subjected to a prolonged inflammation, due to a foreign body, infection, burn or inadequate wound closure, are at risk of abnormal scar formation (10). Occasionally, spontaneous keloids occur without a history of trauma.

Keloids have an increased blood vessel density, higher mesenchymal cell density, a thickened epidermal layer, and increased mucinous ground substance. In keloids, proliferation abnormalities, apoptosis, expression of growth factors and extracellular matrix proteins have been observed. The alpha-smooth muscle actin fibroblasts, myofibroblasts important for contractile situations, are few, if present at all (11). The collagen fibrils in keloids are more irregular, abnormally thick, and have unidirectional fibers arranged in a highly stressed orientation. The increased numbers of fibroblasts recruited to the site of tissue damage synthesize an overabundance of fibronectin, and receptor expression is increased. Mast cell population within keloid scars is also increased, and, subsequently, histamine production increases (12-15).

HISTOLOGY

There are four histologic features that are consistently found in keloid specimens, which are deemed pathognomonic for their diagnosis. These are 1) the presence of keloidal hyalinized collagen, 2) a tongue-like advancing edge underneath normal-appearing epidermis and papillary dermis, 3) horizontal cellular fibrous bands in the upper reticular dermis, and 4) prominent fascia-like fibrous bands (16,17).

CLINICAL FINDINGS

Keloids range in consistency from soft and doughy to rubbery and hard. Early lesions are often erythematous. Lesions become brownish red and then pale as they age. Lesions are usually devoid of hair follicles and other functioning adnexal glands (1).

Once the lesions occur, the clinical course varies. Most lesions continue to grow for weeks to months, and others grow for years. Growth is usually slow, but keloids occasionally enlarge rapidly, tripling in size within months. Once they stop growing, keloids do not usually cause symptoms and remain stable or involute slightly (1).

Keloids may occur anywhere, but the most common locations are the shoulder, presternal area, neck and upper arms. Keloids overlying a joint can contract and restrict movement.

In black persons, the descending order of frequency tends to be earlobes, face, neck, lower extremities, breasts, chest, back and abdomen.

Most patients present with 1 or 2 keloids; however, a few patients, especially patients with spontaneous keloids, have multiple lesions, as do patients who develop keloids as a consequence of acne or chickenpox (19).

THERAPY

No single therapeutic modality has been determined experimentally to be most effective for treating keloid scars. Once they have formed,

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there is no completely satisfactory treatment for keloid. The location, size, and depth of the lesion; the age of the patient; and the past response to treatment determine the type of therapy used (19).

The most important thing to consider in the management of keloid scar formation is prevention. In a patient with a history of keloid scars, all nonessential surgery should be avoided, especially at sites of predilection. In situations in which surgery cannot be avoided, all attempts should be made to minimize skin tension and secondary infection (1). Conventional therapeutic treatment of keloids includes intralesional corticosteroid injections, excisional surgery, radiation therapy, cryosurgery, laser therapy, occlusive dressings, compression therapy and interferon (20). These treatments are reviewed.

Corticosteroids

Corticosteroids, specifically intralesional corticosteroid injections, have been the mainstay of keloid treatment. Intralesional corticosteroid therapy has been used as a sole treatment or in conjunction with surgery or other techniques. The most commonly used corticosteroid is triamcinolone acetonide in concentrations of 10-40 mg/mL administered intralesionally at 4- to 6-week intervals. After several injections with cortisone, the keloid usually becomes less noticeable and flattens in three to six months, but even the best results leave a mark that looks and feels quite different from the surrounding skin (21,22).

Intralesional steroid injections apparently act by diminishing collagen synthesis, decreasing mucinous ground substance, and inhibiting collagenase inhibitors that prevent degradation of collagen, thus significantly decreasing dermal thickening (23). The steroid should be injected into the papillary dermis where collagenase is produced. If the steroid is injected into soft subcutaneous tissue below the keloid, adverse effects may occur (24).

Adverse effects of corticosteroid injections include atrophy of the skin or subcutaneous tissue, hypopigmentation, telangiectasia, necrosis ulceration and visible deposition of steroid in the form of white flecks in the scar. Most of these adverse effects can be avoided by confining injections of the lowest possible dose of steroid to the dermal layer (24).

A typical treatment program of surgery combined with steroids involves injecting steroid into the wound edges after excision and repeating injections into the scar at 6-week intervals for a total of 6 months (20).

Excisional surgery

Surgery is risky, because cutting a keloid can trigger the formation of a similar or even larger keloid. Simple excisional surgery should involve the least amount of soft tissue handling to minimize trauma. The closure with minimal skin tension along relaxed skin tension lines is necessary. In an effort to reduce wound tension, both full- and split-thickness skin grafts have been used, but these have been only partially successful (20). Decreased recurrence rates have been reported with excision in combination with other postoperative modalities, such as radiotherapy, injected IFN, or corticosteroid therapy. Excisional surgery alone has been shown to yield a 45%-100% recurrence rate and should very rarely be used as a solitary modality, although excision in combination with adjunct measures can be curative. Most studies in which excisional surgery was combined with injected steroids report a recurrence rate of less than 50% (25-27).

Radiotherapy

Radiotherapy is not usually considered the treatment of choice for primary keloids, but radiotherapy can be very effective when combined with surgery (28). The most effective time to give radiation therapy is the first 2 weeks after excision, while fibroblasts are proliferating. In recent years, various authors have suggested total doses ranging between 2 and 20 Gy, administered over 1-2 weeks. Postoperative radiation is just as effective as combined preoperative and postoperative radiation (29,30). Some newer studies have shown that high-dose brachytherapy combined with surgical excision can achieve good-to-excellent cosmetic results with an 80%-94% prevention of recurrence. However, some residual hyperpigmentation (5%) and telangiectasias (7%) can occur (31).

Cryosurgery

Cryosurgery is an excellent treatment for keloids that are small and occur on lightly pigmented skin. It is often combined with monthly intralesional corticosteroid injections (20). Cryotherapy uses liquid nitrogen to cause cell damage and to affect the microvasculature, causing subsequent stasis, thrombosis, and transudation of fluid, which result in cell anoxia. Studies that evaluated

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cryotherapy used a protocol of 1-3 freeze cycles lasting for 10-30 seconds, repeating the therapy every 20-30 days. The most common adverse effects of treatment are pain and depigmentation. As a single modality, cryosurgery led to total resolution with no recurrences in 51%-74% of patients after 30 months of follow-up observation. Cryotherapy used in combination with intralesional steroids has an even greater response rate, with objective success reported in 84% of patients (32,33).

Laser therapy

The advantage of laser therapy is that it is a precise, hemostatic excision with minimal tissue trauma, thereby eliminating an excessive inflammatory reaction. The different modes of laser therapy are flash lamp pulsed dye laser, carbon dioxide laser, argon laser, and the Nd:YAG laser. The carbon dioxide laser and argon laser work by similar mechanisms (i.e. by inducing collagen shrinkage through the laser heat). The Nd:YAG laser appears to selectively inhibit collagen metabolism and production. Many studies were performed with these types of lasers over the past 40 years, but none of them proved to be efficacious. All 3 forms of laser therapy, according to multiple studies, have recurrence rates upward of 90% (34-36).

The 585-nm pulsed dye laser (PDL) provides photothermolysis, resulting in microvascular thrombosis. Beginning in the 1980s, the authors noted that scars became less erythematous, more pliable, and less hypertrophic after treatment with 585-nm PDL. The findings were later confirmed using objective measurements of erythema by reflectance spectrometry readings, scar height, and pliability measurements. Because of its efficacy, safety, and relatively low cost, PDL remains the laser treatment of choice for hypertrophic scars. Multiple publications have continued to confirm the role of 585-nm PDL for the treatment of keloids and hypertrophic scars (37-39).

Occlusive dressings

Silicone gel sheets and silicone occlusive dressings have been used with varied success in the treatment of keloids. The sheets can be worn for as long as 12 to 24 h/d for up to 1 year, with care to avoid contact dermatitis and skin breakdown. Antikeloidal effects appear to result from a combination of occlusion and hydration, rather than from an effect of the silicone because the silicone does not appear to enter the skin. Studies have demonstrated that silicone gel increases the temperature of the scar, possibly increasing collagenase activity. Increased pressure, hydration of the stratum corneum, and direct pressure on the wound may also be the modes of action (40-42).

Compression

Mechanical compression dressings have long been known to be effective forms of treatment of keloid scars, especially with earlobe keloids. Compression therapy involves pressure, which has long been known to have thinning effects on the skin. Compression devices are usually custom-made for the patient and are most effective if worn 24 h/d. The patient should start wearing the pressure garment as soon as re-epithelialization occurs and continue wearing it until scar maturation is evident. The mechanism of action is unknown; however, by reducing the oxygen tension in the wound through occlusion of small vessels, subsequent reductions in tissue metabolism, fibroblast proliferation, and collagen synthesis result (43,44).

Interferon therapy

Interferon (IFN) therapy is used in keloid treatment because of its ability to reduce collagen synthesis in dermal fibroblasts. Granstein *et al*. report a 30% reduction in keloid height after intralesional injections of IFN-gamma 3 times weekly for 3 weeks (45). As with other treatment modalities, some recurrences are to be expected. IFN has adverse effects, including low-grade fevers, a flu-like illness for 48-72 hours after injection, and pain on injection (46). Davison *et al*. report that treatment with interferon-alpha was not effective, but interferon combined with intralesional steroid may be beneficial (46,47).

Numerous experimental treatment options for keloids include 5-fluorouracil (5-FU), doxorubicin, bleomycin, verapamil, retinoic acid, imiquimod 5% cream, tamoxifen, tacrolimus, botulinum toxin, and over-the-counter treatments (e.g., onion extract; combination of hydrocortisone, silicone, and vitamin E) (20). Other promising therapies include antiangiogenic factors, including vascular endothelial growth factor (VEGF) inhibitors (e.g., bevacizumab), phototherapy (photodynamic therapy (PDT), UVA-1 therapy, narrowband UVB therapy), transforming growth factor (TGF)-beta3, tumor necrosis factor (TNF)-alpha inhibitors (etanercept), and recombinant human interleukin (rhIL-10), which are directed at decreasing collagen synthesis (20).

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CONCLUSION

There are no more effective treatments for keloids because no clear molecular mechanism is defined for keloid development. The failure of achieving better therapeutic results by the numerous treatments mentioned in this review highlights the essential problem that the pathogenesis of keloids continues to be an enigma for physicians and researchers.

The increased prevalence of keloids paralleling increased cutaneous pigmentation suggests a genetic basis or, at least, a genetic linkage. Trauma to the skin, both physical (e.g., earlobe piercing, surgery) and pathologic (e.g., acne, chickenpox), is the primary cause identified for the development of keloids. The presence of foreign material, infection, hematoma, or increased skin tension can also lead to keloid or hypertrophic scar formation in susceptible individuals. The best way to deal with a keloid is not to get one. A person who has had a keloid should not undergo elective skin surgeries or procedures such as piercing and tattoos. When it comes to keloids, prevention is crucial, because all the current treatments available are often not completely successful or may not work at all. Increased understanding at the molecular level will lead to the development of new therapies. Several of the therapies listed are promising; however, studies thus far have been relatively small in scope, and further investigation is needed in relation to safety, adverse effects, and efficacy of therapy.

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