Hypertrophic Scars and Keloids, Part 1: Conventional Treatments

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Different methods have been described to improve the final cosmetic result of scars. Both preventive and therapeutic measures sometimes require a combination of surgical and medical modalities to achieve a successful treatment plan that ultimately results in the decrease of scar formation, resolution of existent scar, and reduction of recurrence rates. When choosing the most appropriate treatment, physicians should decide on a case-by-case basis, taking into consideration the age and cultural aspects of the patient, as well as the location of the scar, tensional area involved, the size and shape of the scar, and symptoms. Part 1 of this series describes conventional treatments and part 2 discusses newer and investigational therapies for hypertrophic scars and keloids.

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Hypertrophic scars and keloids are the result of an exaggerated response of the skin following injury. These proliferative scars are more common in darker skin types and are characterized by increased collagen, elastin, fibronectin, and glycosaminoglycan contents, as well as low collagenase activity.[1-3]

Hypertrophic scars are raised and stay within the boundaries of the original wound, usually regressing spontaneously. Keloids also are raised but spread beyond the original wound boundaries, invading the surrounding skin; they also may continue to grow over time and often recur following excision. Hypertrophic scars usually are more responsive to different treatment modalities than keloids.[4]

In addition to causing pain, discomfort, and/or pruritus, hypertrophic scars and keloids often are associated with cosmetic concerns related to resultant disfigurement and contractures, which may lead to psychological stress and functional disabilities that ultimately affect the patient's daily life. Although hypertrophic scars and keloids are socially accepted as body art in some cultures,[5] most patients prefer to minimize the appearance of these scars.

The ultimate goal of hypertrophic scar and keloid management is to prevent function impairment and maintain a cosmetically acceptable appearance; therefore, thorough treatment should include different therapeutic options that are appropriate for the patient as well as camouflage techniques to mask skin distortion when results from conventional treatments are not satisfactory.

This article describes therapies that have are proven to be effective in treating hypertrophic scars and keloids and often produce successful cosmetic results. We discuss the most commonly used noninvasive, topical, lasers and radiation, intralesional, and surgical therapies. Additionally, we will review the potential side effects associated with these therapies, which should be considered before choosing the appropriate management option.

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NONINVASIVE THERAPIES

Silicone Dressings

Silicone gel is an effective and well-established therapy that has become the noninvasive standard of care for scar management.[6] The exact mechanism of silicone gel remains both unclear and controversial, but presumed effects include stratum corneum hydration, reduction of evaporation, silicone fluid absorption, oxygen transmission, and increased local temperature[7,8]; other hypotheses suggest inhibition of mast cell activity, increased extracellular matrix formation,[9] and static electrical effects to influence the alignment of collagen deposition.[10]

The reported treatment effects of silicone sheets have been consistent and results from numerous randomized controlled trials demonstrate that it is safe and effective for treatment of hypertrophic scars and keloids. One study compared the effects of intralesional steroid injections versus silicone gel on sternal hypertrophic scars and found that silicone gel sheets provided earlier symptomatic relief, led to more aesthetically pleasing results, and were the preferred treatment among patients with these types of scars.[11] Positive effects from silicone products that have been reported include reduction of erythema, pigmentation, and induration, and an improved overall appearance.[7,12] Silicone gel may be especially useful in patients who cannot tolerate the pain associated with other management procedures.[6]

The efficacy of silicone gel dressings depends on the location of the scar. Certain areas of the body (eg, clavicle, neck, ear, breast, chin, face) do not respond as well as others because it is difficult to keep the gel in contact with the scar surface.[13] The cosmetic effect of this therapy directly depends on early commencement, the grade of response, and patient compliance. Side effects are minimal to nonexistent; however, rashes, pruritus, maceration, and dryness of the skin have been reported.[14]

The addition of vitamin E to the silicone gel has reportedly been successful according to at least 1 randomized blinded study, especially in the short-term prophylaxis of hypertrophic scars or keloids.[15]

Polyurethane dressings have emerged as equivalent or possibly superior alternatives to silicone gel sheets as demonstrated in a randomized trial in which a polyurethane sheet produced a significantly greater effect after 4 and 8 weeks of treatment ($P<.0001$ and $P=.012$, respectively) and was better tolerated than a silicone sheet.[16]

Silicone sheets generally are used in conjunction with other noninvasive treatments as a first-line treatment of minor hypertrophic scars and keloids.[6] Large and recalcitrant hypertrophic scars and keloids usually are treated using more invasive measures; however, silicone sheets may still be used as adjunctive therapy to increase the likelihood of improving scar appearance and symptoms. The recommended use of silicone elastomer sheets is 12 to 24 hours per day for 2 to 3 months, with removal permitted for routine hygiene.[17]

Compression

Compression, or pressure therapy, has been used as a prevention and treatment method for keloids, burn scars, and hypertrophic scars since the 1970s. The mechanism of action is not fully understood, but hypotheses include hypoxia, collagen degradation from decreased levels of chondroitin 4-sulfate, and increased collagenase activity from inhibition of α-macroglobulins.[18] Pressure decreases scar hydration, which stabilizes mast cells, reduces angiogenesis, and decreases extracellular matrix production.[19] Treatment consists of 25 to 40 mm Hg of pressure applied for 12 to 24 hours per day for months to years. An optimal pressure has not yet been elucidated. Pressure therapy alone is recommended for hypertrophic scars without contractures that otherwise would improve with physiologic scar maturation.[20] Compression rarely is used as monotherapy but is used in conjunction with surgery. It most frequently is utilized in the treatment of auricular keloids. Pressure clips typically are used postoperatively for lesions on the earlobe and helix.[21-23] Pressure therapy should be initiated immediately after wound reepithelialization on completion of surgery. Because of the cumbersome nature of its application, patient compliance usually is a limiting factor in obtaining high success rates.

TOPICAL THERAPIES

Imiquimod

Imiquimod is a member of the imidazoquinoline family whose mechanism of action is through toll-like receptors 7 and 8, which are involved in the activation of the immune response[24] and production of inflammatory cytokines such as IFN-α, tumor necrosis factor, IL-6, and IL-12.[25] Additionally, imiquimod promotes apoptosis in human epithelial cells.[26] One of its uses is for the treatment of postsurgical keloids. The best results have yielded from immediate application of imiquimod cream 5% after surgery and continued daily application for 8 weeks.[19]

Recurrence rates associated with postsurgical application of imiquimod have been reported to be as low as 0% at 12 months[27] to as high as 100% within 4 weeks of stopping treatment.[28] This variability partially may result from the different locations of the lesions. For example, keloids on the earlobe and pinna respond better to imiquimod therapy than those on the chest. An example of this difference in results was demonstrated in a study of 45 patients who were treated postexcisionally with imiquimod cream 5% for 8 weeks; the recurrence rate for lesions on the pinna (2.9%) was much lower than lesions on the chest (83.3%).[29]

Local reactions are common, including tenderness and pain on application,[30] erythema, irritation,[31] and transient induration.[27] Follow-up is recommended 1 to 2 weeks after surgery for assessment of local adverse effects.[32] Postinflammatory pigment changes rarely are reported. Systemic adverse effects are infrequent but include flulike symptoms and lymphadenopathy.

Retinoids

Retinoic acid, a vitamin A metabolite that interferes with DNA synthesis, decreases fibroblast proliferation and also may downregulate transforming growth factor β expression.[33-35] Although there is evidence of decreased procollagen production,[35] retinoic acid also has been observed to decrease collagenase production,[34] rendering it an imperfect treatment option. In a small case series, topical tretinoin applied for 12 weeks resulted in decreased weight and size of keloid lesions; however, a reported side effect of irritant contact dermatitis may minimize tolerance.[36]

LASERS AND RADIATION

Lasers

Various lasers, both ablative and nonablative, have been used to treat hypertrophic scars and keloids with varying success. Commonly used ablative lasers include the CO_2 and erbium:YAG (Er:YAG) lasers; nonablative lasers include the pulsed dye laser (PDL) and the Nd:YAG laser.

CO_2 lasers emit light at a wavelength of 10,600 nm, which is strongly absorbed by water in the tissue, producing vaporization. In hypertrophic scars and keloids, the CO_2 laser causes focal necrosis, which leads to collagen remodeling and lesion contraction.[37] The CO_2 laser may be used as monotherapy, but optimal treatment occurs when used in conjunction with intralesional corticosteroids.[38] Intralesional steroids injected at regular 3- to 4-week intervals for up to 6 months demonstrated a lower recurrence rate compared to irregular-interval injections.[38] Adverse events associated with the CO_2 laser include erythema, reversible hyperpigmentation, and permanent hypopigmentation.[39]

The Er:YAG laser emits infrared light at a wavelength of 2940 nm and is more strongly absorbed by water than the CO_2 laser. Commonly used for treating atrophic acne scars, the Er:YAG laser also is useful for treating raised scar borders.[37] A randomized clinical trial found the Er:YAG laser to be effective in improving the elevation and vascularity of hypertrophic scars.[40] The Er:YAG laser also is associated with fewer side effects than the CO_2 laser.

Pulsed dye lasers emit high-energy light at wavelengths of 585 or 595 nm in short pulses. Hemoglobin and oxyhemoglobin within red blood cells have a strong affinity for the emitted wavelength, causing selective photothermolysis of blood vessels, which promotes ischemia and subsequent reduction of scar tissue.[41] There is evidence that PDL activates p38 mitogen-activated kinase, which suppresses scar fibroblast proliferation and type III collagen deposition.[42] Pulsed dye lasers also increase matrix metalloproteinase activity, specifically matrix metalloproteinase 13.[43] One study found that a 585-nm flashlamp-pumped PDL was successful in treating hypertrophic and keloidal sternotomy scars.[44] In patients with darker skin types, successful outcomes were achieved at a longer wavelength of 595 nm after 3 treatments.[45] The addition of cryotherapy spray to the laser therapy increases susceptibility to PDL by improving vascularity.[46]

The Nd:YAG laser emits light at a wavelength of 1064 nm, which suppresses collagen production, likely through inhibition of fibroblasts.[47] In 2 small case-control studies, the Nd:YAG laser was successful in flattening and softening the treated keloids.[48,49] The Q-switched Nd:YAG laser improved the pigmentation, vascularity, pliability, and height of keloids; mild, transient posttreatment erythema was noted.[49] A 532-nm Nd:YAG is more greatly absorbed by oxyhemoglobin, causing larger microvascular changes and decreasing the size of the scar further.[50]

Radiation

Radiation therapy is reserved for hypertrophic scars and keloids that are resistant to other treatments and is believed to function by decreasing fibroblast proliferation via apoptosis induction. Its use as a monotherapy has been found to be ineffective, with recurrence rates of 50% to 100%.[51] Large doses of radiation are required to yield effective results, which increases the risk for developing squamous cell carcinoma.[19] Adjunctive radiotherapy typically is administered 1 to 2 days after surgical excision, but there is insufficient evidence to determine if this regimen increases cure rates.[52] The recommended cumulative dose is 15 to 20 Gy distributed over 5 to 6 treatments.[53] Response rates ranged from 65% to 99%,[52,54] and recurrence rates ranged from 21% to 72%, with most occurring within 13 months of radiation treatment.[52,55] Risk factors for increased recurrence after adjuvant radiation therapy include a keloid with a diameter greater than 2 cm, prior treatment of the keloid, and male gender.[52]

An advantage of radiation therapy is the amelioration of pruritus and tenderness associated with keloid lesions. Adverse effects include hyperpigmentation, ulceration, and erythema.[56] There is concern regarding the use of radiation in pregnant women and children as well as in regions of the body with high carcinogenic potential (ie, breast, thyroid)[57,58]; however, a review concluded that the risk for carcinogenesis from keloid radiation therapy was low with adequate protection of mammary and thyroid glands, making radiation therapy an acceptable treatment modality.[59] Overall, adjunctive radiation therapy is well-tolerated in the treatment of refractory keloids and provides good cosmetic results with minimal side effects.

INTRALESIONAL THERAPIES

Corticosteroids

The mechanism of action for steroids includes the inhibition of inflammatory cell migration, limitation of mitotic activity in fibroblasts and keratinocytes, and reduction of blood supply through vasoconstriction.[60] Steroids also inhibit nitric oxide synthase transcription, leading to the inhibition of collagen synthesis in fibroblasts.[61] The most common steroid used is triamcinolone acetate (TAC) with a dosage that typically includes 2 to 3 injections of 10 to 40 mg/mL administered every 4 to 6 weeks for up to 6 months.[62]

As a monotherapy, intralesional steroids have been successful in reducing the size of keloids, with efficacy rates ranging from 50% to 100%[6]; however, recurrence rates vary from 9% to 50%. It has been demonstrated that a combination of TAC, 5-fluorouracil, and PDL results in better outcomes than TAC monotherapy or combination therapy with TAC 5-fluorouracil only.[63] Intralesional TAC commonly is used postexcision and decreases recurrence rates by an average of 50%.[64]

Despite their effectiveness in reducing the size and recurrence of keloids, corticosteroids are associated with adverse effects that also must be considered, including pain on injection, which may be reduced with the coadministration of intralesional lidocaine[65]; telangiectases; necrosis; ulcerations; skin and subcutaneous fat atrophy; and hypopigmentation.[66] Patients should be advised that hypopigmentation resulting from intralesional steroid therapy may be permanent.[19]

Bleomycin

Bleomycin is a polypeptide antibiotic isolated from a strain of *Streptomyces verticillus*[67] with antitumor, antibacterial, and antiviral properties.[4] In addition to blocking the cell cycle, inhibiting DNA and RNA, and producing reactive oxygen species,[68] bleomycin also reduces collagen synthesis, increases degradation secondary to the inhibition of lysyl oxidase and transforming growth factor β1, and induces fibroblast apoptosis.

To our knowledge, few relevant studies have investigated the efficacy of bleomycin in the treatment of hypertrophic scars and keloids. A recent technique for delivering bleomycin to these lesions is called bleomycin tattooing in which multiple punctures are made on the keloid or hypertrophic scar with a 25-gauge needle and bleomycin (2 mL/cm^2) is dripped onto the lesion.[4] In one randomized controlled trial, the relative mean resolution score in the bleomycin tattoo group was approximately 88%, with a complete response observed in 47% of patients. Another clinical trial suggested bleomycin to be superior in flattening keloids when compared with cryotherapy and intralesional triamcinolone. The resulting therapeutic effects appear greatest in keloids with a volume greater than 100 mm^2.[4]

Locally applied bleomycin results in minimal side effects, with transient hyperpigmentation and mild to moderate local pain among the most common. Complications such as ulceration are rare. This treatment modality is easy to administer and is moderately priced.[69]

Interferon

Intralesional interferon is a cytokine with antifibrotic, antiviral, and antiproliferative properties. Interferon interferes with collagen synthesis and fibroblast proliferation,[70] increases collagenase activity, and inhibits overproduction of collagen and glycosaminoglycans by fibroblasts.[39] Intralesional interferon also acts through transforming growth factor β1 modulation, further inhibiting proliferation and fibrosis.[71]

Interferon may be used as monotherapy or as adjunctive therapy. Results from trials of interferon as monotherapy have shown inconsistent and unconvincing results[70-73]; however, as postoperative therapy or in combination with other treatment methods, interferon seems to be more promising. One study found that recurrence rates were lowest in patients treated postoperatively with interferon alfa-2b (18.7% [3/16]) compared with those treated with TAC (58.4% [38/46]) and those who received no adjuvant therapy (51.1% [22/43]).[74] The recommendation for postoperative interferon injection is 1,000,000 U/cm of skin surrounding the postoperative site administered immediately after surgery and then 1 to 2 weeks thereafter.[19] In combination with other modalities such as intralesional TAC and the CO_2 laser, the addition of interferon alfa-2b lowers recurrence rates and leads to better outcomes.[75,76]

Adverse effects that have been reported include flu-like symptoms,[70] which can be prevented by pretreatment with acetaminophen.[77] Other unfavorable reactions include pain on injection, local erythema, and edema.

SURGICAL THERAPIES

Cryosurgery

The low temperature induced by cryosurgery causes vascular injury and stasis of blood flow to the keloid, leading to cellular anoxia, tissue necrosis, and detachment.[78] Treatment recommendations include two 15- to 20-second thaw cycles performed on each visit every 3 weeks for a total of 8 to 10 visits.[19]

Response to cryosurgery has been reported as high as 80%.[78,79] Newer keloids that are more vascular are more susceptible than chronic keloids and respond better to cryosurgery than to treatment with intralesional TAC.[79] The combination of cryosurgery with intralesional corticosteroids is superior to either treatment alone.[80] One study found that this combination therapy produced an 84% positive response rate.[81] Lesions treated with combination therapy require fewer procedures and have lower recurrence rates.[82] Intralesional cryosurgery also has demonstrated successful results, showing 51.4% reduction in scar volume after just 1 treatment session.[83] It also resulted in fewer permanent pigmentation changes.[84]

Immediate local complications associated with cryosurgery include pain, stinging sensation, edema, and bulla formation,[82] which can be prevented with anesthetic cream.[80] Other adverse effects include atrophy, necrosis, and hypopigmentation and hyperpigmentation, which may persist for several years following treatment.[19,85] The risk for pigment abnormalities is related to the duration of freezing as well as the number of sessions.[78] A freeze/thaw time that exceeds 25 seconds may lead to destruction of melanocytes, thereby causing hypopigmentation, and should be avoided to achieve cosmetically successful results.[19] Cryosurgery results in less scarring compared to other surgical procedures.[86,87]

Surgical Excision

Surgical excision is the most practical and effective method for keloid removal and is indicated for large scars, scars containing painful furuncles, scar contractures compromising musculoskeletal function, and scars unlikely to respond to noninvasive therapies.[88] Excising the abnormal hypertrophic tissue creates a new wound where new collagen begins to form; unfortunately, a larger and more aggressive keloid can recur in its place. Surgical removal is not recommended as monotherapy because of the high recurrence rate (45%–100%).[89,90]

In combination with other treatment modalities, the recurrence rate is 8% to 50%.[91] Preoperative and/or postoperative intralesional corticosteroids are added to the surgical approach, rendering good results and decreasing recurrence rates, but preoperative steroids can interfere with stitch placement and wound healing.[92]

Excisional therapy also is used in combination with pressure dressings, interferon injections, and radiation therapy; these combinations all have shown promising results.[19,93-95]

There are many methods for scar removal, including simple scar revision, resurfacing with skin grafts, local or even distant flaps, intrascar excision, geometric broken line closure, and dermabrasion.[92,96] Tangential shaving leads to better healing and reepithelialization, rendering superior cosmetic outcomes with less recurrence.[97,98]

Surgical treatment frequently is limited by lack of adequate soft tissue available for reconstruction. When treating large scars surgically, one of the best techniques is afforded by tissue expansion through the implantation of tissue expanders, which gives abundant amounts of same tissue to be utilized in the surgical repair.[96] Z-plasty, W-plasty, and V-Y and Y-V advancement flaps are some of the techniques currently used to remove keloids.[92,98-100]

CONCLUSION

When choosing the most appropriate treatment of hypertrophic scars and keloids, physicians should decide on a case-by-case basis, considering the patient's age as well as the location of the scar, tensional area involved, size and shape of the scar, and symptoms. The noninvasive, topical, lasers and radiation, intralesional, and surgical therapies described here have demonstrated promising results. Part 2 will discuss newer and investigational therapies.

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