The Most Current Algorithms for the Treatment and Prevention of Hypertrophic Scars and Keloids

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Background: Previous reports on the treatment of hypertrophic scars and keloids have not described clear algorithms for multimodal therapies. This article presents an evidence-based review of previous articles and proposes algorithms for the treatment and prevention of hypertrophic scars and keloids.

Methods: The methodologic quality of the clinical trials was evaluated, and the baseline characteristics of the patients and the interventions that were applied and their outcomes were extracted.

Results: Important factors that promote hypertrophic scar/keloid development include mechanical forces on the wound, wound infection, and foreign body reactions. For keloids, the treatment method that should be used depends on whether scar contractures (especially joint contractures) are present and whether the keloids are small and single, or large and multiple. Small and single keloids can be treated radically by surgery with adjuvant therapy (which includes radiation or corticosteroid injections) or by nonsurgical monotherapy (which includes corticosteroid injections, cryotherapy, laser, and antitumor/immunosuppressive agents such as 5-fluorouracil). Large and multiple keloids are difficult to treat radically and are currently only treatable by multimodal therapies that aim to relieve symptoms. After a sequence of treatments, long-term follow-up is recommended. Conservative therapies, which include gel sheeting, taping fixation, compression therapy, external and internal agents, and makeup (camouflage) therapy, should be administered on a case-by-case basis.

Conclusions: The increase in the number of randomized controlled trials over the past decade has greatly improved scar management, although these studies suffer from various limitations. The hypertrophic scar/keloid treatment algorithms that are currently available are likely to be significantly improved by future high-quality clinical trials. (Plast. Reconstr. Surg. 125: 557, 2010.)

Many articles have suggested that there are effective ways to treat abnormal scarring of the skin, including hypertrophic scars and keloids, but the use of these treatments and their effectiveness when used in various combinations remain to be clearly defined. Consequently, an evidence-based review of the relevant literature was performed, and the diagnosis, prevention, and treatment of hypertrophic scars and keloids are discussed here. At present, it is still difficult to know the effectiveness of various treatments for hypertrophic scars and keloids because of variations between studies in terms of the race, age, and sex of the participating patients; the anatomical area that is affected; the size of the lesion(s); the ways that treatment outcomes and response rates are measured; the follow-up term; and whether patient satisfaction is measured. Despite these limitations in the current literature, there was sufficient information to design the keloid/hypertrophic scar treatment algorithms that are proposed in this article (Figs. 1 and 2). If the necessary evidence-based knowledge was missing or inadequate, this is indicated to make it clear where additional high-quality clinical trials that will improve the treatment algorithms are needed.
DIFFERENTIAL DIAGNOSIS OF HYPERTROPHIC SCARS AND KEOIDS

The pathogeneses of keloids and hypertrophic scars are not well understood. Many traditional textbooks classify hypertrophic scars and keloids as completely different types of scars. Clinicians define hypertrophic scars as scars that do not grow beyond the boundaries of the original wound, whereas keloids grow horizontally. In contrast, pathologists distinguish keloids from hypertrophic scars histologically on the basis of thick eosinophilic (hyalinizing) collagen bundles that are absent in hypertrophic scars. However, there are also many cases where the scar bears the growth and histologic features of both hypertrophic scars and keloids (Fig. 3). There is also the possibility that hypertrophic scars and keloids are manifestations of the same fibroproliferative disorder of

Fig. 1. Treatment algorithms for hypertrophic scars (HSs).
the skin that is expressed by a continuum of features. However, alleged hypertrophic scars improve naturally and gradually, although the full maturation process may take up to 2 to 5 years, whereas alleged keloids do not resolve naturally. Because these features shape how they should be treated, they should be defined as shown in Table 1, and scars that bear features of both hypertrophic scars and keloids should be considered and treated as keloids.

EXCLUDING THE POSSIBILITY THAT THE LESIONS ARE ATTRIBUTABLE TO SIMILAR-LOOKING DISEASES

Gulambuseinwala et al. reported a pathologic analysis of 568 scars that revealed the absence of malignancies or dysplasias. Therefore, they concluded that routine histologic analysis of scars is not necessary. Wong and Lee have argued against this approach, saying that malignant or local destructive tumors can be misdiagnosed clinically as
keloids. Indeed, malignant tumors, including dermatofibrosarcoma protuberances and giant cell fibroblastomas, have been mistaken for hypertrophic scars or keloids in previous reports. Furthermore, our analysis of 378 patients who had been diagnosed with hypertrophic scars/keloids and treated in our facility revealed that 1.06 percent of the lesions were actually caused by other diseases although, fortunately, all of the diseases were benign. Thus, we recommend that the parameters listed in Table 2 be reviewed before planning treatment for suspected keloids/hypertrophic scars (Fig. 1, A, and Fig. 2, A).

**Table 1. Differential Diagnosis of Hypertrophic Scars and Keloids**

Pathologists distinguish keloids from hypertrophic scars histologically on the basis of thick eosinophilic (hyalinizing) collagen bundles that are absent in hypertrophic scars. These conditions can also be defined clinically on the basis of their growth patterns. However, clinicians and pathologists still have conflicting views regarding the differential diagnosis of these conditions.

- **Hypertrophic scar**: A fibroproliferative disorder of the skin that does not grow beyond the boundaries of the original wound.
- **Keloid**: A fibroproliferative disorder of the skin that grows beyond the boundaries of the original wound or has an unrecognized origin.

**Table 2. Excluding the Possibility That the Lesions Are Caused by Similar-Looking Diseases**

The following parameters should be considered before the treatment of keloids/hypertrophic scars is planned.

1. A biopsy should be conducted in anomalous cases.
2. Corticosteroid injections should be performed only after carefully excluding the possibility that malignancies or infections may be present.
3. It should be remembered that it is particularly challenging to accurately differentially diagnose African Americans because the color of their skin scars and tumors is often similar.

**PREVENTION OF HYPERTROPHIC SCARS AND KELOIDS**

Hypertrophic scars occur when there are major skin wounds, including those resulting from surgery, trauma, and burns. In contrast, keloids can arise from very small injuries or weak inflammation processes, including acne and injections. Consequently, special care should be taken when treating patients who have a history of keloids. Risk factors that promote the development of hypertrophic scars and keloids, and that can be limited by physicians, are mechanical force (stretching tension) on the wound, wound infections, and foreign body reactions (Table 3).
Table 3. Key Points for Preventing Hypertrophic Scar and Keloid Development

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<th>Key Points</th>
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<td>1. Avoid excessive movements that stretch the wound, and use bandages and</td>
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<td>appropriate garments</td>
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<td>2. Avoid subjecting the wound to direct mechanical force (e.g., friction,</td>
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<td>scratching) and use gel sheeting and taping.</td>
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<td>3. For patients with earlobe wounds, minimize contact with pillows when</td>
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<td>lying down to avoid friction.</td>
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<td>4. For female patients with chest wounds, tight brassieres and underwear</td>
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<td>should be worn to avoid the skin-stretching tension caused by the weight</td>
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<td>of the breasts.</td>
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<td>5. For patients with suprapubic wounds, a belly-warmer tie or garment is</td>
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<td>recommended.</td>
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<td>6. After surgery and injury, the wound should be kept clean by means of</td>
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<td>irrigation and application of antibacterial/antimycotic agents.</td>
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<td>7. After surgery and injury, contact of the wounded dermis (including ear-</td>
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<td>lobe piercing) with foreign bodies should be avoided.</td>
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Mechanical Force (Skin Stretching Tension)

It is well known that hypertrophic scars/keloids occur frequently on particular sites, including the anterior chest, shoulder, scapular area, lower abdomen, suprapubic region, and earlobe. These sites all have in common the fact that they are frequently subjected to skin stretching caused by the natural daily movements of the body. In contrast, hypertrophic scars/keloids occur very rarely on the scalp and the anterior lower leg, where bones lie directly under the skin and the skin is rarely subjected to stretching tension. This site-specificity of hypertrophic scars/keloids suggests that to prevent the development of keloids and hypertrophic scars, it would be useful to avoid subjecting wounded skin to sustained mechanical force, thereby permitting the wound to rest and heal normally. Supporting this is the fact that keloid growth patterns can be simulated by computer analysis of skin-stretching tension. Moreover, Aarabi et al. recently described an animal model of hypertrophic scars where hypertrophic scar–like lesions developed when mechanical force was applied to wounds on the backs of mice.

To limit skin stretching during healing and thereby facilitating appropriate wound resting, wounds should be covered by fixable materials, including tape, bandages, garments, or silicone gel sheets. Supporting this is a study by Atkinson et al., who reported a randomized controlled trial of the effect of tape fixation on the prevention of hypertrophic scars after cesarean section in 70 subjects. They found that scar volume decreased significantly when paper tape was used. The randomized controlled trial of Gold et al. also showed that silicone gel sheeting significantly reduces the incidence of hypertrophic scars or keloids in high-risk subjects with a history of abnormal scarring. The randomized controlled trial of Chan et al. also revealed that silicone gels may be able to prevent the development of hypertrophic scars after sternotomy-associated wounding. However, when O’Brien and Pandit conducted a meta-analysis of 13 trials involving 559 individuals, they found that there was only weak evidence that silicone gel sheeting can prevent abnormal scarring in high-risk individuals. Further randomized controlled trial studies will be necessary to elucidate this issue fully.

Wound Infections and Foreign Body Reactions

Both infections and foreign body reactions prolong the inflammation process associated with wound healing. It is likely that infections and foreign body reactions induce the abnormal secretion of proinflammatory mediators that in turn prompt abnormal responses by fibroblasts. Thus, it is crucial that wounds are kept clean by means of irrigation after surgery and injury. Moreover, the contact of wounded dermis (including in earlobe piercing) with foreign bodies should be avoided.

TREATMENT OF HYPERTROPHIC SCARS

Hypertrophic scars become obvious within weeks after injury, after which they rapidly increase in size for 3 to 6 months. Then, after a static phase, they begin to regress. However, for those hypertrophic scar cases with scar contractures (especially joint contractures) that could result in functional dysfunction, surgery is indicated.

Surgery

Releasing scar contractures improves joint function and also accelerates the maturation of surrounding immature scars and hypertrophic scars (Fig. 1, B). Small and linear hypertrophic scars can be treated by complete surgical resection (Fig. 1, C) or nonsurgical multimodal therapy (Fig. 1, D). In these cases, a type of tension-releasing technique, which includes Z-plasty, W-plasty, and small wave incision, should be applied to prevent the recurrence of hypertrophic scars. Intractable recurrent hypertrophic scars should be treated according to the keloid treatment algorithm, where the combination of surgery and adjuvant therapy is the treatment of choice (Fig. 1, E, and Fig. 4).

With regard to suture materials, the randomized controlled trial performed by Luck et al.
revealed that absorbable and nonabsorbable sutures do not differ significantly in terms of the rates at which facial hypertrophic scars form. However, when Durkaya et al.\textsuperscript{26} performed a similar randomized controlled trial, this time on hypertrophic scars that develop after midline sternotomy incision, they found that the use of nonabsorbable sutures diminished the risk of hypertrophic scars. Thus, the choice of suture materials depends on the site of application, with nonabsorbable sutures being more suitable for high-skin-tension sites such as the anterior chest wall.

**Nonsurgical Therapies**

Hypertrophic scars without scar contractures improve naturally during the process of scar maturation (Fig. 5). However, various nonsurgical therapies can accelerate this process and improve the subjective symptoms. Thus, it is recommended that hypertrophic scars without scar contractures should be treated by one or more of the multiple nonsurgical therapies available, especially the noninvasive therapies, which include compression therapy and gel sheeting (Fig. 1, D).

**Compression Therapy**

The randomized controlled trial of Chang et al.\textsuperscript{27} that examined the effectiveness of pressure therapy in 122 cases found that when pressure garment–treated and untreated groups were compared in terms of their average age, surface area of the burn on the body, length of hospital stay, or time to wound maturation, significant differences between the groups were not observed. However, when Van den Kerckhove et al.\textsuperscript{28} performed a similar randomized controlled trial, but more precisely measured the pressure applied, they found that pressure garments that deliver a pressure of at least 15 mmHg tend to accelerate scar maturation. The mechanisms by which pressure can accelerate scar maturation should be elucidated. In the meantime, it seems that applying appropriate amounts of pressure on hypertrophic scars could be a useful therapeutic technique.

**Gel Sheetling**

Gel sheeting therapy can be used in two settings, namely, to prevent hypertrophic scars after surgery and to treat hypertrophic scars.\textsuperscript{19} Regarding the latter application, Maján\textsuperscript{29} reported a randomized controlled trial that revealed that patients treated with soft silicone dressings showed greater and more rapid improvement in hypertrophic scar maturation than untreated patients. Moreover, the randomized controlled trial conducted by Li-Tsang et al.\textsuperscript{30} indicated that silicone gel sheeting helps to reduce the thickness, pain, itchiness, and rigidity of severe hypertrophic scars.

Regarding the materials from which gel sheets are made, de Oliveira et al.\textsuperscript{31} examined the effec-
tiveness of nonsilicone gel sheeting in their randomized controlled trial and concluded that silicone and nonsilicone gel dressings are equally effective. Akaishi et al.32 used a computer analysis to show that silicone gel sheeting reduces the tension on the hypertrophic scar. They concluded that it is vital that gel sheets are soft and elastic. However, So et al. 33 reported that improved patient education increases their compliance in silicone gel sheeting therapy, as patients participating in an improved education program had significantly better ratings regarding scar border height and thickness at 6 months than the conventionally educated patients. These observations suggest that hypertrophic scars are most effectively treated with gel sheets if the patients are properly educated, whereas the type of material used to construct gel sheets may be a less important factor.

Corticosteroid Injection

It has been suggested that synthetic corticosteroids decrease the production of inflammatory cytokines, chemokines, adhesion molecules, lysosomal enzymes, and tissue inhibitor of metalloproteinase, and inhibit fibroblast proliferation.34 However, the disadvantages of corticosteroid treatment include severe pain caused by the injection and systemic side effects that include menstrual dysfunction in women, the suppression of adrenal cortical function, and the development of cataracts or glaucoma. The local side effects include thinning and atrophy of the skin and subcutaneous tissues, development of steroid acne, capillary dilatation, and hypopigmentation. These complications can hamper the use of corticosteroids in combination treatments. Indeed, corticosteroid-based treatment of hypertrophic scars requires careful planning with the patient. An international panel of experts that reviewed the available clinical literature has recommended that corticosteroid doses of 2.5 to 40 mg per site should be used,2 but additional randomized controlled studies are needed to determine the appropriate site-specific dose.

Laser

Wittenberg et al.35 and Alster36 reported randomized controlled trials examining the efficacy of pulsed dye laser therapy combined with silicone gel sheeting and steroid injection, respectively, but found that these combination therapies did not yield significant effects. However, pulsed dye laser irradiation alone effected a substantial clinical and histologic improvement. The randomized controlled trial performed by Allison et al.37 also suggested that pulsed dye laser is an effective treatment for the intense pruritus that is often experienced during the healing process after a burn injury. However, this study did not reveal other significant benefits, including reductions in scar redness or improvements in the height and texture of the scar. Manuskiatti and Fitzpatrick38 reported that pulsed dye laser applied at a pulse width of 0.45 msec was more effective in decreasing scar size and

![Fig. 5. Naturally healing hypertrophic scars. (Left) Granulation tissues immediately after the burn wounds were sustained. (Center) Hypertrophic scars 2 years after the burn wounds were sustained. (Right) Mature scars 5 years after the burn wounds were sustained; hypertrophic scars without scar contractures improve gradually during the process of scar maturation, despite minimal noninvasive treatment being applied. However, textural improvements take longer to manifest.](image-url)
improving scar pliability than a pulse of 40 msec. In conclusion, pulsed dye laser on its own may be useful for treating hypertrophic scars.

**Others**

Invasive treatments, including cryotherapy and 5-fluorouracil injections, should not be used to treat hypertrophic scars, although they may be effective with keloids (see below). However, noninvasive external and internal agents such as ointments and gels, tape, and nonsteroidal antiinflammatory drugs are useful for treating hypertrophic scars, although their effects are limited because they mainly reduce subjective symptoms (e.g., itching and pain).

Corticosteroid ointments, tape, and nonsteroidal anti-inflammatory drugs have been shown to be effective in reducing symptoms, but further randomized controlled trials are required to fully elucidate the therapeutic potential of these agents. Several randomized controlled trials have been performed to test the benefits of onion extract gels and mugwort lotion, but these agents do not seem to improve objective symptoms.

Oral administration of another internal agent, namely, the antiallergic drug tranilast, appears to reduce the symptoms of hypertrophic scars. It is well known that tranilast also effectively reduces the rate of restenosis of coronary arteries (which is a type of fibrosis similar to hypertrophic scars) after percutaneous transluminal coronary angioplasty. Thus, this drug is promising as a hypertrophic scar therapy.

Finally, to manage the psychological stress of patients, makeup or camouflage therapy should be considered, as these therapies improve not only the cosmetic appearance of the scars, but also reportedly promote physiologic changes. This issue warrants scientific study.

**TREATMENT OF KEOIDS**

Unlike when hypertrophic scars are treated, the size and number of keloid lesions should be determined before planning the treatment. In other words, are the keloid lesions small and single or large and multiple? This categorization is necessary because small (early) and single keloids can be treated radically (Fig. 2, B), which is an approach that has been facilitated by the improvement in our understanding of adjuvant therapies after primary surgery (Fig. 2, D). Several therapeutic approaches, including laser treatment, are also effective as monotherapies in the radical treatment of early keloids (Fig. 2, E). Nonsurgical conservative therapies alone do not seem to be effective for treating keloids. In particular, careful discussions and goal-setting with patients are essential steps in the management of large and multiple keloids (Figs. 2 and 6, below, left). Patients with such keloids usually have major problems, including infections (e.g., inclusion cysts) and pain. Consequently, mass reduction surgery (Fig. 2, F) and symptomatic multimodal therapies (Fig. 2, G) can be considered on a case-by-case basis.

**Surgery**

Surgery can be used to treat keloids in two ways: first, radically resecting keloids (Fig. 2, D); and second, reducing keloid mass (Fig. 2, F). Radical resection should be combined with adjuvant therapy because keloid excision alone is associated with a high rate of recurrence (45 to 100 percent). With regard to the mass reduction approach, it should be used only to remove infected regions and to reduce enough of the keloid(s) to effect symptomatic improvement. Adjuvant therapy after mass reduction surgery is not recommended because this could lead to excessive exposure to radiation or the side effects of corticosteroids.

**Corticosteroid Injections**

Corticosteroid injections can be used to treat keloids in three ways: first, as an adjuvant therapy that is to be combined with surgery (Fig. 2, D); second, as a monotherapy for the radical treatment of keloids (Fig. 2, F); and third, as a component of multimodal therapy for the treatment of symptoms (Fig. 2, G). In a prospective trial performed by Kiil, 52 patients were treated with triamcinolone injections alone, whereas 15 patients received the steroid therapy together with keloid excision. The combined treatment and injection therapy alone were similarly effective. However, partial recurrence was observed in one-third of the cases after 1 year, regardless of the treatment that had been applied, whereas after 5 years, the recurrence rate was 50 percent. Muneech et al. reported that corticosteroid injection monotherapy had beneficial long-term outcomes, with 82 percent of 63 patients experiencing an improvement in subjective symptoms. Combining corticosteroid injections with 5-fluorouracil, pulsed dye laser, and cryotherapy has been reported to be more beneficial than corticosteroid injection monotherapy, although there are too few randomized controlled trials testing these issues to be able to draw solid conclusions.

**Cryotherapy**

Cryotherapy has been used to treat keloids either as a monotherapy or in combination with intralesional triamcinolone injection. Cryotherapy de-
livery methods include contact,56 sprays,55–57 and intralesional needles.58,59 Layton et al.60 found from their randomized controlled trial that early, vascular lesions responded to cryosurgery significantly better than larger lesions. It should be noted that cryotherapy should be limited to small regions, as it induces severe pain and hypopigmentation.

The mechanism by which cryotherapy reduces keloids is very interesting. It is well known that hypertrophic scars and keloids occur on burned skin areas but not on frostbitten areas. It appears that although burning and frostbite both induce apparent tissue necrosis, they induce the secretion of quite different proinflammatory mediators; the response to these inflammatory signals by the fibroblasts may also differ. Further basic research should be performed to elucidate these mechanistic discrepancies.

Fig. 6. Typical severe keloids: (above, left) 9 years ago, (above, right) 5 years ago, (below, left) 2 years ago, and (below, right) in their current state. Keloids grow not only vertically but also horizontally. In the case presented here, the various keloids grew over 9 years to the point they had merged. However, the central area of the keloid mass has become depressed and become mature scar.

Radiation
Combining surgery with postoperative radiation therapy has been suggested to more effectively treat keloids than radiation monotherapy.61 The success rate of this combined approach varies between 67 and 98 percent,62 although few randomized controlled trials have been performed to test the effectiveness of this technique. In many institutions, radiation is initiated right after surgery, and the total dose is limited to 20 Gy over several administrations.23,24,47 Guix et al.46 described keloid treatment using high-dose-rate brachytherapy and concluded that it treats keloids more effectively than superficial x-ray or low-energy electron beam administration.

An important concern associated with keloid radiation therapy is the risk of inducing malignant tumors. However, in the reported cases where malignant tumors arose after keloid radiation
therapy, it remains unclear whether the radiation therapy involved appropriate radiation doses and adequate protection of the surrounding tissues, especially the mammary glands and thyroid. To address this issue, Leer et al. performed a questionnaire-based study in which radiation oncologists in 508 facilities throughout the world were asked about the indications of radiation therapy for keloids. The radiation oncologists in 78 percent of the facilities replied that keloids are an accepted indication for radiation therapy. Moreover, of the 77 facilities located in the United States and Canada, over 90 percent found that radiation therapy for keloids is acceptable. It should be noted that plastic surgeons generally avoid radiation therapy for benign tumors, including keloids, for fear of inducing malignant tumors. The latter study suggests that surgeons should perhaps liaise more closely with radiation oncologists before excluding the possibility of radiation therapy for keloids.

Antitumor/Immunosuppressive Agents

Uppal et al. and Nanda and Reddy have reported randomized controlled trials that tested the efficacy of 5-fluorouracil for treating keloids. The keloid scar scores of the majority of patients improved by more than 50 percent after 5-fluorouracil treatment. Haurani et al. found from studying a prospective case series (n = 32) that intralocal 5-fluorouracil treatment after surgery prevented recurrence, as the recurrence rate was 19 percent at the 1-year follow-up. The authors recommended the use of 50 mg per session, with a total exposure of 500 mg. However, Fitzpatrick and Gupta and Kalra have reported using up to 150 mg per session, with total doses being between 1200 and 2400 mg. Further work to determine the appropriate dose should be initiated.

Naeini et al. have reported that bleomycin is effective in treating keloids, and the randomized controlled trial of Broker et al. revealed that interferon therapy is also effective. However, Davison et al. reported that their randomized controlled trial of interferon α-2b showed it was not effective in treating the 39 keloids examined and they concluded that it is not useful for the clinical management of keloids. These therapies should be studied by additional randomized controlled trials.

LONG-TERM FOLLOW-UP OF HYPERTROPHIC SCARS AND KEOIDS AFTER TREATMENT

It is important that sequentially treated hypertrophic scar and keloid patients are followed up over the long-term and are appropriately educated about managing their scars (Fig. 1, F and Fig. 2, H). With regard to hypertrophic scars, it is important that wounds are not subjected to mechanical force (skin-stretching tension) and are allowed to rest by using gel sheeting or tape fixation, and that these measures be sustained until the hypertrophic scars become mature scars. With regard to massage therapy for hypertrophic scars, Patiño et al. reported that it did not appreciably improve the vascularity, pliability, or height of hypertrophic scars, although a decrease in pruritus was observed in some patients. Thus, there is little evidence that suggests massage accelerates hypertrophic scar maturation.

CONCLUSIONS

Many plastic surgeons, especially those in non-Caucasian societies, avoid treating abnormal scars because of their high frequency of recurrence. However, over the past decade, many more randomized controlled trials addressing abnormal scar management and treatment have been performed. This means there is now sufficient evidence-based information for us to start devising standard international algorithms of abnormal scar treatment. Here, algorithms for the treatment of hypertrophic scars and keloids have been proposed. However, these algorithms should be optimized for each human race. They are also likely to improve significantly as our knowledge of scar biology progresses, higher quality clinical trials are performed, and new agents to treat scars are developed.

REFERENCES


