Topical treatments for hypertrophic scars

Joanna M. Zurada, AB,a David Kriegel, MD,b and Ira C. Davis, MDc

New York, New York

Hypertrophic scars represent an abnormal, exaggerated healing response after skin injury. In addition to cosmetic concern, scars may cause pain, pruritus, contractures, and other functional impairments. Therapeutic modalities include topical medications, intralesional corticosteroids, laser therapy, and cryosurgery. Topical therapies, in particular, have become increasingly popular because of their ease of use, comfort, noninvasiveness, and relatively low cost. This review will discuss the properties and effectiveness of these agents, including pressure therapy, silicone gel sheeting and ointment, polyurethane dressing, onion extract, imiquimod 5% cream, and vitamins A and E in the prevention and treatment of hypertrophic scars. (J Am Acad Dermatol 2006;55:1024-31.)

The wound healing process consists of 3 stages—inflammation, granulation, and matrix remodeling.1,2 The first phase, inflammation, produces exudate from damaged vessels that fills the wound. Neutrophils trigger an inflammatory cell cascade and macrophages phagocytose cellular and foreign debris. Subsequently, in the granulation phase, macrophages secrete cytokines that promote granulation tissue formation consisting of re-epithelialization, recreation of an appropriate blood supply, and reinforcement of the injured tissue. In the final stage of wound healing, matrix remodeling, fibroblasts proliferate and deposit new collagen and matrix materials at the wound site. The remodeling process of collagen synthesis and lysis can last up to 2 years after tissue injury.

Hypertrophic scars, by definition, represent an exaggerated proliferative response to wound healing that stays within the boundaries of the original wound, in contrast to keloids, which have a more aggressive life cycle and extend beyond the original borders. Because the collagen found is in a disorganized, whorl-like arrangement rather than in the normal parallel orientation, hypertrophic scars are indurated, elevated, and poorly extensible.1 Hypertrophic scars are also characterized by hypervascularity, hence, their erythematous appearance.

Clinically, hypertrophic scars are raised, red, nodular lesions that occur most commonly in areas of thick skin. They frequently develop within 8 weeks of a burn, wound closure with excess tension, wound infection, hypoxia, or other traumatic skin injury.1,3 Their normal course involves a rapid growth phase for up to 6 months that may be followed by regression during the next 12 to 18 months.3

Early recognition of the potential development of the hypertrophic scar is critical in its management. Because hypertrophic scars are often painful and difficult to treat, several treatments have been developed in the past several years in an effort to minimize tissue growth and wound contraction. This review will focus on pressure therapy, silicone gel sheeting and ointment, polyurethane dressing, onion extract, imiquimod 5% cream, and vitamins A and E in the management of hypertrophic scarring. A summary of these therapies and a selection of common commercial products can be found in Tables I and II, respectively.

PRESSURE THERAPY

Pressure therapy has been the preferred conservative management of scars since the 1970s, especially in treating hypertrophic scarring after burn injury. Pressure therapy is influential primarily while the scar is active and, therefore, loses some efficacy after 6 months of treatment.4 The garments are typically custom-made from an elastic material with a high spandex content and are intended to be worn for approximately 1 year until the scar matures.5 To prevent a decrease in elasticity, garments should be changed every 6 to 8 weeks. Drawbacks of compression therapy include its limited use in anatomic depressions, flexures, or areas of high movement; patient discomfort; the need to be
worn at all times; and occasional skin ulceration from uneven pressure distribution. For these reasons, patient compliance can be a major problem, with reports of noncompliance ranging from 8.5% to 59%.6,7

Pressure treatment is believed to accelerate wound maturation by several mechanisms, namely a thinning of the dermis, decrease in edema, and a reduction of blood flow and oxygen.1 The hypoxic environment is hypothesized to decrease collagen formation and increase collagen lysis and loosen the collagen fibrils aligned to the skin surface, thereby more closely approximating the elastic requirements.

Table I. Topical scar therapies

<table>
<thead>
<tr>
<th>Product</th>
<th>Preparation</th>
<th>Use</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure therapy4-13</td>
<td>Custom-made elastic compression garment</td>
<td>Worn all day until scar is mature; new garment made every 6-8 wk</td>
<td>Low cost</td>
<td>Limited use on face, anatomic depressions, or high-motion areas; low patient compliance; subjective pressure measurements; side effects of local skin maceration</td>
</tr>
<tr>
<td>Silicone gel sheeting3,14-29</td>
<td>Soft, extensible tacky, or nontacky gel sheet</td>
<td>12-24 h/d for 2-4 mo</td>
<td>Easy to use, more effective than silicone gel alone</td>
<td>Cumbersome application, especially in areas of movement; side effects of superficial maceration</td>
</tr>
<tr>
<td>Polyurethane dressing30-35</td>
<td>Self-adhesive, flexible polyurethane pad</td>
<td>12-24 h/d for 2-4 mo</td>
<td>Breathable</td>
<td>Cumbersome application, especially in areas of movement</td>
</tr>
<tr>
<td>Onion extract36-39</td>
<td>Transparent topical gel</td>
<td>3-4 times/d for 8 wk on new scars (after wound closure) and 2-6 mo on old scars</td>
<td>Good for exposed areas, widespread availability</td>
<td>Few documented effects on scars</td>
</tr>
<tr>
<td>Imiquimod 5% cream40-43</td>
<td>Cream</td>
<td>Once every 3-4 d for 8 wk</td>
<td>Infrequent application</td>
<td>Side effects of acute inflammatory reaction (pruritus, erythema, burning); prescription only; costly</td>
</tr>
<tr>
<td>Topical vitamin A45-48,56</td>
<td>Various creams</td>
<td>Daily application; no established duration</td>
<td>Easy to use, good for exposed areas</td>
<td>Potential systemic absorption causing hypervitaminosis or birth defects</td>
</tr>
<tr>
<td>Topical vitamin E49-55,57</td>
<td>Various creams</td>
<td>Daily application; no established duration</td>
<td>Easy to use, good for exposed areas</td>
<td>Side effects of contact dermatitis and theoretic scar widening</td>
</tr>
</tbody>
</table>

Studies have shown: −, no adequate benefit; −/+ or equivocal results; +, some benefit; ++, marked benefit.
of the skin. This hypothesis remains controversial, however, as other studies have shown that qualitative improvements in scar tissue receiving pressure therapy correlate with increased blood flow.

A fair body of evidence supports the use of compression therapy but literature is generally lacking in reports on effectiveness and optimal pressures. The consensus is that an applied pressure of 25 mm Hg may represent ideal loading, but more recent studies suggest that good clinical results may be achieved at much lower compression levels. However, given that most often this measurement is made clinically by the therapist together with feedback from the patient, pressure measurements are subjective and not standardized. Overall, there is some evidence to support that compression therapy may be effective but more definitive research is needed to evaluate the most optimum parameters.

**SILICONE GEL SHEETING AND OINTMENT**

Silicone, a soft, semiocclusive scar cover, is composed of cross-linked polydimethylsiloxane polymer that has extensibility similar to that of skin. Since its introduction in 1982, topical silicone gel sheeting and ointment have been used widely to minimize the size, induration, erythema, pruritus, and extensibility of pre-existing hypertrophic scars and to prevent the formation of new ones. Numerous formulations exist, in addition to several gels and ointments (Table II).

The therapeutic effect of topical silicone gel sheeting on pre-existing hypertrophic scars is well documented. Although there have been several uncontrolled clinical reports stating that silicone gel sheeting promotes resolution of hypertrophic scars, a number of more valid controlled studies exists. For example, in a controlled trial of 20 patients who had either evolving hypertrophic scars or keloids, silicone gel sheeting stopped the development of and softened evolving hypertrophic scars or keloids, silicone gel sheeting controlled trial of 20 patients who had either evolving scars, a number of more valid controlled studies exists. Silicone sheets are effective in reducing the development of abnormal scars after surgical excision. Five patients had a history of hypertrophic scar formation and were given silicone sheeting within 2 months of operation to prevent recurrence. In 11 of these cases (79%), hypertrophic scars did not recur after at least 6 months of follow-up.

The mechanism of silicone gel sheeting remains unclear, although several hypotheses exist. Studies have shown that silicone sheets do not change pressure, temperature, or oxygen tension at the wound site. Silicone sheets have an evaporative water loss almost half that of skin and have been compared with the stratum corneum. Most researchers believe that silicone acts by creating a hydrated, occluded environment that decreases capillary activity, thereby reducing fibroblast-induced collagen deposition and scar hypertrophy. Silicone sheets decrease hyperemia and minimize fibroblast production of collagen and promote wound flattening. Interestingly, the use of silicone cream alone compared with silicone cream with occlusive dressing showed 22% and 82% scar improvement, respectively, with respect to erythema, tenderness, pruritus, and hardness. These results supported that occlusion may be synergistic in wound healing and suggested that silicone gel alone may not be as effective as silicone sheeting.

Wounds treated with silicone gel sheeting have negligible amounts of silica in histologic sections. Therefore, the presence of silicone itself may not be necessary. A randomized controlled study showed that silicone gel dressings and nonsilicone gel dressings were equally effective in improving size, induration, and color of hypertrophic scars. In another study comparing a silicone-free cream and occlusive dressing with petrolatum alone, scar improvement was significantly greater in the cream-occlusive dressing group with respect to pruritus, pain, hardness, elevation, and erythema, further supporting this hypothesis.

In summary, silicone gel sheeting is efficacious, both in minimizing the severity of hypertrophic scars in fresh wounds and in promoting the resolution of pre-existing hypertrophic scars. Silicone ointment
or gel, although more convenient and suitable for exposed areas, is less effective than silicone sheeting.

**POLYURETHANE DRESSING**

Polyurethane dressing is a self-adherent, flexible, hydroactive pad that should be worn 12 to 24 h/d for a minimum of 8 consecutive weeks. Advantages of this form of treatment are its availability as clear pads for use on exposed areas such as the face or hands and low incidence of skin maceration because of the pads’ evaporative properties. Polyurethane occlusive dressings act by creating a moist wound-healing environment that may promote re-epithelialization and dermal extracellular matrix synthesis and, hence, decrease scarring. Despite the theoretic risk that a moist environment is associated with a higher risk of wound infection, studies have shown that occlusive dressings do not increase the incidence of infection. Hydroactive dressings have been shown to prevent the formation of hypertrophic scars. A pilot study of 60 patients noted significant improvements in microcirculation and surface qualities in patients who were treated with polyurethane dressing for
6 weeks after surgical incisions when compared with other patients who were randomized to receive either dry gauze dressing until removal of the sutures, hydroactive dressing until removal of the sutures, or dry gauze dressing until removal of sutures followed by hydroactive dressing for 6 weeks.\textsuperscript{35} In another study of 60 patients with acute facial lacerations, a 5-day course of polyurethane dressing after acute skin injury—despite initially showing significantly improved comfort, less erythema, and less potential for scarring when compared with dry gauze—showed negligible differences between the dry gauze control group after 2 months.\textsuperscript{33} This suggested that the magnitude of benefit from occlusive dressings may depend on long-term treatment.

Polyurethane dressing also reduces color, prominence, and hardness of mature hypertrophic scars.\textsuperscript{10,30} In a comparative study in which 12 patients were randomized to 4 groups (hydroactive polyurethane dressing alone, polyurethane plus compression, silicone sheeting plus compression, and compression alone for 24 h/d for 8 weeks), the most pronounced effects were achieved with either polyurethane dressing plus compression or silicone sheeting plus compression.\textsuperscript{10} Polyurethane plus compression was slightly superior to silicone plus compression in reduction of surface roughness. These effects lasted for at least 1 year after the termination of therapy. Furthermore, polyurethane dressing alone was found to provide functional and structural improvement in scar tissue that was slightly superior to that obtained from compression alone. It was speculated that scar dressings and compression may promote dynamic shear forces needed for tissue reorganization.

Currently, polyurethane dressing has unclear effects on the development of new hypertrophic scars but has been shown to improve the prominence and appearance of mature scars in a small randomized trial. Further studies are necessary to elucidate its role in hypertrophic scar treatment.

**ONION EXTRACT**

_allium cepa_, or onion extract, is found in a number of scar treatment products. Patients, in particular, value this remedy because of its ease of use, relatively low cost, “botanical” ingredients, and widespread availability. Onion extract exhibits anti-inflammatory, bacteriostatic, and collagen down-regulatory properties\textsuperscript{36} and improves collagen organization in a rabbit ear model.\textsuperscript{37}

Documented clinical studies of onion extract have shown that onion extract does not improve hypertrophic scarring. To date, there have been 3 major controlled clinical studies in the United States on the effect of onion extract on human wound healing.

One clinical trial evaluating onion extract in the prophylactic treatment of 17 scars after Mohs micrographic surgery showed no statistically significant difference between pretreatment and posttreatment evaluations of erythema and pruritus after 1 month of 3-times daily applications of onion extract gel.\textsuperscript{38} In fact, a significant reduction in scar erythema was demonstrated in control patients who used a petrolatum-based ointment for 1 month, possibly because of the effects of petrolatum on scar hydration.

Another randomized, double-blinded trial evaluating 97 patients with new and old scars who were assigned to a Mederma treatment group or placebo gel control group for 2 months showed similar results. Scar changes were measured using 6 categories of scar size, overall improvement, noticeable appearance, elevation, erythema, and softness. The only significant advantage in the treated group was the patient-reported improvements of a softer, less noticeable scar at 2 months.\textsuperscript{39} There were no notable differences with respect to physician-measured appearance and size nor patient-measured erythema and elevation. More patients in the placebo group than treated group reported improvement with a less noticeable scar at 1 week and a less red scar after 1 month. The study’s short follow-up time of 2 months, however, was a limitation of this study.

The most recent randomized, double-blinded, split-scar study of 24 patients with new surgical wounds also demonstrated that onion extract gel did not improve scar appearance, erythema, and hypertrophy when compared with a petrolatum-based ointment.\textsuperscript{40} Before enrollment, each patient tested negatively for an allergic reaction to both treatments by a 48-hour patch test on the forearm. Each scar half then received either the onion extract or petrolatum ointment 3 times daily for 8 weeks. The scars were evaluated by blinded investigators and patients at 2, 8, and 12 weeks after initiation of treatment and by blinded patients at 11 months postoperatively. None of the scars became hypertrophic at 11 months, but it was uncertain whether the patients would have developed abnormal scarring without treatments. One limitation of this study, however, was that all the patients were elderly Caucasians, a group inherently at lower risk for hypertrophic scarring than patients who are younger and have darker skin.

In summary, despite the wide use of onion extract by patients, there is no evidence that it is beneficial in improving hypertrophic scars. In the few studies conducted to date, more patients in the petrolatum control group reported greater improvements in
wound healing when compared with those who used onion extract.

**IMIQUIMOD 5% CREAM**

Imiquimod 5% cream, a topical immune response modifier, is approved for treatment of genital warts, basal cell carcinoma, and actinic keratoses. Imiquimod stimulates proinflammatory cytokines, especially interferon-α, which generate a cell-mediated immune response. Interferon-α increases collagen breakdown. In addition, imiquimod alters the expression of genes associated with apoptosis. Therefore, imiquimod has been used in an attempt to reduce keloid recurrences after excision. Studies with imiquimod consisted of gently rubbing the cream over the scar for 3 to 5 minutes once every 3 to 4 days for a period of 8 weeks. At 24 weeks postsurgery, imiquimod treatment improved scar quality, especially color and elevation, when compared with two control groups (no treatment and treatment with petrolatum). There was an absence of hypertrophic scars and keloids in the imiquimod group, although this might have been related to the small sample size. Of note, all patients in the treatment group experienced an inflammatory response characterized by erythema, local pain, and pinpoint bleeding. This response allowed “blinded” physicians to distinguish between treatment and control groups that may have biased the results.

In summary, imiquimod has been shown to improve hypertrophic scar quality after operation in a preliminary small, randomized, prospective clinical trial, but additional studies with a larger sample size and longer follow-up are necessary to determine the role of imiquimod 5% cream in hypertrophic scar therapy.

**VITAMIN A**

Vitamin A is required to maintain the integrity of epithelial and mucosal surfaces. Based on the observation that oral vitamin A improved the appearance of keloid scars, it has been tested in the form of 0.05% retinoic acid in wound healing. Daily application of retinoic acid to intractable hypertrophic and keloid scars has been shown to reduce size and pruritus and cause scar softening, flattening, and fading of color. In a randomized, double-blind study, Daly et al demonstrated a statistically significant 20% reduction in scar size in the 0.05% retinoic acid treatment group compared with the base cream control group. A more recent study of a different form of vitamin A, 0.25% tocoeretinate ointment, showed marked decreases in the size, stiffness, erythema, and pruritus in all mature hypertrophic scars. Only 4 hypertrophic scars were examined, however, making these data preliminary.

Vitamin A treatment has its downsides, however. As topical retinoids may be absorbed systemically, hypervitaminosis and teratogenicity are potential complications of this form of therapy and, therefore, limit its use, especially in pregnant women and people who take oral vitamin supplements.

In general, sufficient data are lacking on the efficacy of topical vitamin A on hypertrophic scarring and its use may be associated with side effects. Vitamin A should, therefore, not be recommended.

**VITAMIN E**

Vitamin E (tocopherol), a lipid-soluble antioxidant, has complex effects on wound healing. It has been shown to penetrate into the reticular dermis and reduce the formation of oxygen radicals that impede healing and damage DNA, cellular membranes, and lipids. Vitamin E also alters collagen and glycosaminoglycan production and inhibits the spread of peroxidation of lipids in cellular membranes, thereby acting as a membrane-stabilizing agent.

Despite numerous anecdotal reports claiming that vitamin E speeds wound healing and improves the cosmetic appearance of scars, little scientific evidence exists to support these claims. Jenkins et al, in an attempt to reduce scarring after reconstructive surgery in patients with burn, used topical vitamin E in the postoperative period. No significant differences were found in range of motion, scar thickness, change in graft size, and overall cosmetic appearance between the vitamin E treatment group and base cream control group 1 year after surgery. In addition, 20% of patients reported local reactions to the vitamin E cream. A subsequent double-blind, placebo-controlled clinical trial evaluating patients who applied emollient with vitamin E and emollient alone to each half of their scar from Mohs micrographic surgery (twice daily for 4 weeks starting soon after surgery) also demonstrated similar results. Twelve weeks after surgery, vitamin E did not help in improving the cosmetic appearance of scars or was detrimental in appearance in 90% of cases. A high incidence (33%) of contact dermatitis was noted. Limitations of the study included the use of the d-a-tocopheryl form of vitamin E, which has been widely associated with contact dermatitis, and
the potentially diluted concentration of topical vitamin E (one crushed capsule of 320 IU in 1 g of emollient).

The use of vitamin E in scar management has other theoretic limitations. Because of its ability to inhibit collagen synthesis, the use of vitamin E early in scar therapy may reduce scar tensile strength and, hence, lead to the development of widened scars and even wound dehiscence.55

When used in conjunction with silicone gel sheets, however, vitamin E has been shown to improve pre-existing hypertrophic scars. In all, 38 patients (95%) who received silicone gel sheets with added vitamin E improved by at least 50% with respect to color, size, and cosmetic appearance, whereas only 30 patients (75%) using silicone gel sheets alone improved at least 50% after 2 months of treatment.56 This study led to the conclusion that the combination of vitamin E and silicone gel sheeting is beneficial in hypertrophic scar treatment, possibly as a result of a synergistic effect.

In conclusion, the evidence that topical vitamin E alone improves the cosmetic appearance of scars is poor. It is also associated with a high incidence of contact dermatitis. The use of vitamin E should, therefore, be discouraged.

DISCUSSION

Studies of scar treatments to date are limited for a number of reasons. A suitable animal model is lacking. Many studies on scar treatments did not use controls,3,18,21-24 used other confounding methods such as pressure or intermittent corticosteroid injections,10,15,19 or applied different methods of scar assessment, making it difficult to evaluate the precise effects of each topical treatment. The studies also varied in the ages of scars studied and used different control protocols, such as no treatment or emollient massage. Another long-standing issue has been the difficulty to quantitatively measure certain subjective scar parameters, such as color, induration, or pruritus. Given the long-term and sometimes cumbersome nature of scar treatment, patient compliance has also been problematic. Finally, because of the unclear clinical distinction between hypertrophic scars and keloids, several studies combined the two entities;5,17-21,24-27 however, these two scar types have very different histologic features, growth patterns, and responses to treatment. On this note, because hypertrophic scars sometimes spontaneously regress, the beneficial qualities attributed to the various treatments may actually be partially caused by natural healing.

Several other topical treatments that are occasionally used in an attempt to minimize hypertrophic scars lack enough scientific data regarding their effect on this type of scar. Such topical therapies include aloe vera, vitamin C, corticosteroids, and tacrolimus. A new patent-pending product, a botanical QR340 formula (Quigley Pharma, Doylestown, Pa), has preliminarily demonstrated higher efficacy than Mederma and placebo in hypertrophic scar improvement. Further studies are necessary to determine these products’ role in hypertrophic scarring.

In conclusion, there is no single, optimal modality that can eliminate or prevent hypertrophic scarring. Currently, the most accepted treatment for old and new hypertrophic scars is silicone gel sheeting. Silicone ointment or gel alone, however, is less effective than silicone sheeting. Pressure therapy has demonstrated some efficacy but is cumbersome and not standardized. Polyurethane dressing has equivocal effects on the development of new hypertrophic scars but may improve the appearance of mature scars. Products in the United States containing onion extract do not improve scar cosmesis or symptomatology when compared with a petrolatum-based ointment. Imiquimod 5% cream has been shown to improve the quality of new hypertrophic scars after surgery in a preliminary clinical trial, but further studies are necessary. Vitamin A lacks sufficient data and may be associated with side effects, especially in pregnant women. Finally, vitamin E alone may be detrimental to wound healing and often leads to contact dermatitis; it should, therefore, not be recommended.

REFERENCES