Emerging Therapies for Scar Prevention

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Significance: There are ~12 million traumatic lacerations treated in the United States emergency rooms each year, 250 million surgical incisions created worldwide every year, and 11 million burns severe enough to warrant medical treatment worldwide. In the United States, over \$20 billion dollars per year are spent on the treatment and management of scars.

Recent Advances: Investigations into the management of scar therapies over the last decade have advanced our understanding related to the care of cutaneous scars. Scar treatment methods are presented including topical, intralesional, and mechanical therapies in addition to cryotherapy, radiotherapy, and laser therapy.

Critical Issues: Current treatment options for scars have significant limitations. This review presents the current and emerging therapies available for scar management and the scientific evidence for scar management is discussed.

Future Directions: Based upon our new understanding of scar formation, innovative scar therapies are being developed. Additional research on the basic science of scar formation will lead to additional advances and novel therapies for the treatment of cutaneous scars.

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SCOPE AND SIGNIFICANCE

SCAR FORMATION, although evolutionarily beneficial in wound healing, can create a substantial aesthetic and functional burden. There are an estimated 12 million traumatic lacerations treated in the United States emergency rooms each year, 250 million surgical incisions created worldwide every year, and 11 million burns severe enough to warrant medical treatment worldwide.^{1,2} In this review, an overview of both established technologies and emerging therapies for scar prevention and management are presented.

TRANSLATIONAL RELEVANCE

The management and treatment of cutaneous scars is a major burden

in healthcare. Over \$20 billion dollars are spent annually on the treatment and management of scars. The majority of the literature on scar management is experiential or case-based, with few prospective, translational studies published. This review presents the current and emerging therapies available for scar management. Limitations in the scientific literature regarding scar management are discussed.

CLINICAL RELEVANCE

Problematic scar formation can result in painful, functionally limiting, and disfiguring scars. Patients are highly concerned about scarring even following routine surgery, and the vast majority of patients value

any improvement in their scarring. Techniques and technology in scar management and, ideally, prevention has therefore become a field of innovation and clinical research. This review highlights the clinically relevant therapies available for the treatment and management of scars.

DISCUSSION OF FINDINGS AND RELEVANT LITERATURE

Topical scar therapies

Onion extract (*extractum cepae*). Onion extract, or *extractum cepae*, is used as a topical agent to reduce scar formation. It has both bactericidal and anti-inflammatory properties, thought to be mediated via the flavonoids quercetin and kaempferol inhibiting fibroblast proliferation and collagen production.⁴ It is primarily used as a prophylactic treatment against excessive scar formation after surgery or laser tattoo removal. In a recent review of the literature, evidence for the efficacy of onion extract was found to be inconsistent. In some studies, it was found to improve scar symptoms and appearance, but it was not more efficacious than a petroleum-based emollient control, and was less efficacious than silicone gel or silicone sheeting.^{5,6} However, when used in combination with other therapies its therapeutic effect is enhanced versus either silicone gel sheeting or intralesional corticosteroid injections alone.^{5,7,8} In a prospective study, significant improvement in cosmesis, induration, pigmentation, and tenderness of scars were found using onion extract versus controls.^{5,9} In a retrospective cohort study, improvement of erythema, pruritis, and consistency of hypertrophic scars was found when comparing onion extract versus intralesional corticosteroid injections; furthermore, fewer adverse events were noted.^{5,10} A consistent finding is that the use of onion extract is well tolerated, both when used alone and in combination with other agents. Greater patient satisfaction has also been found when using onion extract versus placebo or other lotion.⁵ Recommendations based on this evidence can therefore be made to consider onion extract an adjunct in treating symptomatic hypertrophic scars or for postoperative prophylaxis.^{4,5}

Mitomycin C. Mitomycin C is a natural compound isolated from *Streptomyces* species that acts to cross-link DNA, preventing DNA replication and thus cell reproduction. It has been used topically and intravenously, as a chemotherapeutic agent.¹¹ The available evidence for mitomycin C is very limited. In a case series of two patients, marked reduction in the size and height of keloids after treatment with

shave excision, topical mitomycin C application, and radiation therapy was achieved with no recurrence with 2 year follow-up.¹¹ In another small series, no keloid recurrence was seen after surgical excision and topical mitomycin C treatment with 6–24 month follow-up.¹² However, a different investigation showed keloid worsening and ulceration development after treatment with intralesional mitomycin C.¹³ Overall, there is not enough quality evidence to render a recommendation on the use of mitomycin C for scar management.

Imiquimod. Imiquimod 5% cream is an immune response modifier that stimulates interferon to increase collagen breakdown, and it also alters the expression of apoptosis-associated genes.¹⁴ There is some evidence in small, nonrandomized studies that the use of topical imiquimod cream reduced the rate of keloid recurrence after surgical excision, particularly lesions on or near the earlobe.^{15–20} Interestingly, however, this same success was not seen in truncal keloids, with a reported high rate of recurrence after surgical excision and imiquimod therapy.²¹ Unfortunately, a prospective, double-blind, placebo-controlled trial failed to demonstrate any significant reduction in keloid recurrence rates when using imiquimod versus placebo after keloid excision.²²

Intralesional scar therapies

Bleomycin. Bleomycin is an intralesionally injected agent that is thought to inhibit collagen synthesis via decreased stimulation by transforming growth factor-beta 1 (TGF- β 1).⁴ The evidence for bleomycin therapy is fairly limited, with only small and variably designed studies in the literature. These studies suggest a significant improvement in hypertrophic scar or keloid height and consistency, reduction of erythema, pruritus, and pain.^{23–25} One study demonstrated a superior therapeutic response when compared with cryotherapy combined with intralesional triamcinolone.²⁴ Side effects noted include depigmentation and dermal atrophy.⁴ Due to the nature of this agent and its antineoplastic functionality, it has the potential to be a systemically toxic agent; however, systemic toxic effects of bleomycin injected intralesionally appear to be quite rare.²⁶

Interferon. Interferon decreases synthesis of collagen I and III, while also having antiproliferative effects.^{15,23,26,27} When injected into a lesion, interferon has been shown to reduce keloid size by 50% after 9 days, which is superior when compared with intralesional corticosteroid therapy.²⁷

Hypertrophic scars also show good response to interferon treatment; when injected three times per week, significant improvement in scar quality and volume was noted.²⁸ Interferon treatment can cause systemic flu-like symptoms, and local inflammatory reactions at the injection site.^{4,5} Furthermore, interferon therapy is quite costly, and the current evidence does not appear to justify the use of this treatment in most cases where other treatment options are available.²⁹

Corticosteroids. Intralesional injections of corticosteroids have been a mainstay of treatment for keloids and hypertrophic scars. It is the preferred first-line treatment for keloids and the second-line treatment for hypertrophic scars.^{26,30} Intralesional injection of triamcinolone acetonide acts by promoting collagen degradation and inhibiting fibroblast growth, therefore inhibiting collagen production.²⁶ This mechanism is especially important in keloid scars because keloid fibroblasts produce three to four times as much collagen as normal skin cells or nonpathologic scar fibroblasts.³⁰ The recommended treatment protocol is a total of three to four injections of triamcinolone acetonide, 10–40 mg/mL every 3–4 weeks; however, some scars require longer treatment.³¹ Response rates from a wide array of studies are reported from 50% to 100%.^{3,4,26} Recurrence rates are reported from 9% to 50%, compared to recurrence rates after excision alone reported as 45% to 100%.²⁶ Side effects of corticosteroid injection include hypopigmentation, dermal atrophy, and telangiectasia; these side effects may be lessened by using low doses of steroids combined with other forms of therapy.²⁶ Combination with intralesional cryotherapy, discussed below, appears to have the greatest efficacy, particularly with regard to scar thickness and pruritis.^{4,5,32}

Unfortunately, intralesional corticosteroid injection is often a painful procedure, and may be poorly tolerated by pediatric patients. Some practitioners therefore have reported using topical corticosteroid application under an occlusive dressing to improve trans epidermal absorption. Unfortunately, topical absorption through intact epidermis into the deep dermis is limited, and studies have shown no reduction in scar formation after burn injury using topical corticosteroids.²⁶ There are some data demonstrating greater efficacy of topical corticosteroid compared with placebo in improving hypertrophic scar and keloid appearance and tenderness, in addition to data demonstrating ~50% improvement of keloids using a combination of topical corticosteroid with

fractional ablative laser treatments, although this still involves a potentially painful procedure.^{33,9} Unfortunately, there are no data comparing the effectiveness of topical corticosteroid application using occlusive dressings versus intralesional corticosteroid injection.

Botulinum toxin A. Botulinum toxin A (BTA) has been used both as a prophylactic treatment to improve wound surgical incision healing and as an intralesional treatment for keloids. A classic surgical principle to improve surgical incision healing is to close the skin under as minimal of tension as possible. The mechanism of action for BTA is to paralyze the muscle fibers into which it is injected; by reduction of intrinsic muscle tension, the mechanical forces on a wound are decreased, thus reducing skin tension on the incision. BTA therapy has been investigated in the improvement of surgical scars by injecting into the musculature adjacent to the surgical wound either up to 7 days prior or up to 24 h after the surgery, and has been shown to demonstrate improved wound healing with less noticeable scars compared with placebo.^{4,34} When studying the intralesional injections of keloids, there have been mixed results. One study reported excellent to fair results in a series of 12 patients into which BTA was injected at a concentration of 35 U/mL into established keloids every 3 months for up to 9 months. Scar regression, flattening of the edges of the lesions, and no evidence of recurrence was noted at 1 year follow-up.³⁵ However, another study demonstrated no evidence of keloid improvement using objective evaluation via optical profilometry.³⁶ Decreased fibroblasts and TGF- β 1, as a consequence of decreased tensile forces, was initially proposed as the mechanism of action for intralesional injection of BTA into mature scars, but in subsequent investigations no *in vitro* effects could be found demonstrating BTA effect on TGF- β 1 or fibroblast proliferation.^{35,36}

Cryotherapy

Cryotherapy has historically been limited to scars small in size due to the need for repeated treatments, prolonged healing times between treatments, skin atrophy, pain, and the potential for permanent pigment alterations.⁵ However, new techniques have been developed to improve the efficacy and applicability of cryotherapy. As discussed above, the combination of cryotherapy with intralesional corticosteroid injection shows greater improvements in thickness and symptoms of keloids and hypertrophic scars when compared with either treatment used alone.³² The proposed mechanism of this greater efficacy is that cryo-

therapy induces dermal edema, allowing greater corticosteroid penetration and volume deposition into the target tissues.^{4,5} Even more recently, intralesional cryotherapy has been demonstrated as a superior modality when compared with traditional contact cryotherapy. In this technique, a probe is inserted into the hypertrophic scar or keloid, and liquid nitrogen is injected into the tissue, effectively freezing and destroying the scar tissue cells from the inside out.^{37,38} An average of scar volume reduction of 51% was reported following a single cryogenic treatment, with significant alleviation of clinical symptoms.^{4,37,38}

Radiotherapy

Brachytherapy, X-ray, and electron beam forms of radiotherapy have all been employed in the treatment of scar management, usually as adjunct therapy or a secondary treatment. Ionizing radiation works by inhibiting proliferating fibroblasts, therefore decreasing the pathologic deposition of collagen.^{29,39} Additionally, radiation induces apoptosis in lymphocytes, differentiation of fibroblasts, and various intracellular changes to induce an anti-inflammatory effect and ultimately hypocellular, devascularized tissue.²⁹ The goal is to reduce the overactive cell growth and collagen deposition of pathologic scar formation without inhibiting cell growth to such a degree that it inhibits wound healing. Typically, radiotherapy has been combined with surgical excision as a modality to reduce keloid recurrence.^{4,5,29} Recommended treatment protocol is to start radiation therapy (conventional radiotherapy, electron therapy, or brachytherapy) no more than 24 h after surgical excision of the keloid; recommended radiation dose is 2 Gy applied every 1–2 days for a total dose of no more than 12 Gy in 6 or 10 fractions.²⁹ Side effects include hyper- or hypo-pigmentation, dermal atrophy, erythema, telangiectasias, and skin dryness. These are uncommon when total dose is less than 12 Gy.^{4,29} Caution is recommended when considering radiation therapy for scars on the anterior neck or chest, given the risk of thyroid or breast carcinogenesis.^{4,5}

Laser therapy

Two main forms of laser therapy have been investigated in the use of scar treatment: ablative and nonablative. Ablative lasers seek to flatten pathologic scar tissue by ablating tissue through high energy transfer to the tissue via either the continual-wave CO₂ (cw-CO₂) laser or the pulsed erbium:yttrium-aluminum-garnet (Er:YAG) laser.²⁹ Nonablative lasers, predominantly the fractionated pulsed dye laser (585 or 595 nm wavelength)

selectively destroy microvascularization in the scar tissue, causing necrosis of the vascular supply of the scar tissue and ultimately hypoperfusion and subsequent hypoxia, resulting in regression of the scar.²⁹ Additionally, intracellular alterations including reduction in TGF- β 1 expression and therefore fibroblast proliferation and collagen production, upregulation of matrix metalloproteinase-13 (MMP-13, a collagenase) and therefore collagen degradation, and induction of fibroblast apoptosis have been described after treatment with pulsed dye laser (PDL).^{4,29} Side effects, when they occur, are usually mild and consist of erythema, edema, temporary purpura, temporary or permanent hypopigmentation, or hyperpigmentation, blistering, or pruritis.^{4,5,40,41}

Evidence regarding the efficacy of laser treatment on surgical scars, hypertrophic scars, and keloids is somewhat mixed, but overall shows good results when the correct therapy is chosen for a particular indication. Multiple studies report significant improvement in scar thickness, erythema, pruritus, and texture when the appropriate laser treatment has been utilized; these studies have examined surgical scars, hypertrophic scars, keloids, and burn scars.^{42,43,44} PDL (585–595 nm) reduces hyperemia and edema of the immature burn scar. Fractional CO₂ laser (10,600 nm) corrects abnormal texture, thickness, and stiffness of more mature scars. Intense pulsed light/broad band light improves burn scar dyschromia and mild persistent inflammation. Alexandrite laser (755 nm) destroys in-grown hair follicles and obstructed sweat glands.⁴¹ Furthermore, the sequence of laser therapy is important. PDL used first in immature scars with hyperemia works to selectively coagulate the microcapillaries and reduce the inflammatory response within the local environment of the scar. The fractionated 10,600 nm CO₂ laser used next ablates columns of scar tissue, allowing new collagen to re-form, ideally in a more organized fashion.⁴¹

When treating keloids with ablative lasers, recurrence rates have been reported to be as high as 92%, and monotherapy is not recommended.⁴⁵ However, risk of recurrence is reduced when combined with other therapies such as pressure therapy, intralesional corticosteroid injection, cryotherapy, or radiation therapy.^{29,46} Additionally, cw-CO₂ laser treatment may be considered as a monotherapy when aiming to debulk or ablate nonactive hypertrophic scars.⁴ When using ablative lasers, the cw-CO₂ laser is used for removing larger volumes of scar tissue, or when attempting to remove scar tissue that is hard, due to its efficacy at removing tissue

and in achieving hemostasis.²⁹ When treating or removing scar tissue that is a smaller volume, or in sensitive areas, Er:YAG laser is recommended due to its ability to spare the surrounding tissue due to its athermic nature.²⁹

Mechanical therapy

Silicone. Silicone treatments are well established in the armamentarium of scar management, however, new formulations are emerging as better alternatives to the sometimes difficult to manage silicone sheeting. Originally, it was thought that silicone had intrinsic antiscar properties. Although the mechanism of silicone-based therapies has not been definitively elucidated, it appears likely that at least part of the mechanism involves occlusion, hydration, and the retention of increased moisture under the silicone dressing to improve hydration in the stratum corneum, which in turn may have downstream effects on fibroblast activity via keratinocyte-mediated epidermal-dermal signaling pathways.^{47,48} Silicone-based treatments have been shown to improve the volume, elasticity, color, and firmness in hypertrophic scars and keloids.^{4,5,48–50} When used prophylactically on surgical incisions, it can prevent the development of pathologic scars.^{51–53}

Silicone gel sheets were the mainstay of silicone-based treatments until relatively recently. Unfortunately, these sheets could be difficult to use, particularly in large areas, in areas near or over joints, and in areas with high degrees of contour variability, such as the face. However, newer iterations of silicone gel sheeting are now available that are more pliable, adhesive, and durable. Additionally, other formulations of silicone-based treatments have been developed that have similar efficacy to silicone gel sheeting. Silicone oil-containing cream is easier to apply than sheeting, particularly to highly contoured areas. It has been shown to have similar effects as silicone gel sheeting, but only when combined with an occlusive dressing; when used without an occlusive dressing, it has significantly less effect on scar improvement.⁵⁴ A second new formulation is silicone gel that is applied topically like an ointment that then dries into a flexible gas-permeable but water-impermeable sheet. It has been shown in multiple studies to be as effective as silicone gel sheeting, but again is clearly more easily applied to highly contoured areas.^{55–57} For any type of silicone treatment, recommendations are to use the silicone application 12 h/ per day for 12–24 weeks.

Pressure therapy. Pressure therapy uses compression dressings to deliver mechanical pressure to the scar, reducing capillary perfusion pressure and

accelerating collagen maturation, with the goal of flattening the scar.^{4,5,29} It has been used for many years as standard of care for preventing and treating burn scars.⁵ Unfortunately, compression garments can be uncomfortable and unsightly, leading to difficulties with patient compliance. Furthermore, no clear benefit was found by a meta-analysis, just a very slight reduction in scar height.⁵⁸ Some studies have found benefit to using various pressure-applying instruments such as pressure buttons on pathologic scars of the ear.^{59,60} Higher pressure, from 20 to 30 mmHg, has been shown to be much superior when treating hypertrophic scars when compared with lower pressure of 10–15 mmHg.⁶¹

Pressure garments should be initiated early in the scar maturation process and should be worn at least 23 h per day for at least 6 months while the scar is still active.⁴ Certainly the wound must be epithelialized, but benefit is noted even in the early stages of scar hyperemia, such as in burn scars.²⁹ Garments can take the shape of bandages or elastic sleeves, gloves, stockings, suits, and even face masks.

Scar massage is a form of pressure therapy that is thought to work both by accelerating collagen maturation as discussed above, and by influencing scar remodeling by disrupting fibrotic tissue, improving pliability, and reorienting the collagen fibers.⁶² Scar massage is a very commonly recommended therapy for scar flattening and softening and anecdotally seems to work. Despite this, because there are innumerable scar massage regimens, inconsistent outcome measures, and few comparative studies, there is only weak evidence supporting the use of scar massage to improve scar height, firmness, and appearance; however, a recent literature review did find some evidence that scar massage appears more effective specifically for postsurgical scars.⁶²

Adhesive microporous hypoallergenic paper tape. It is a core surgical principle to close wounds under as little tension as possible to minimize risk of wound healing complications. There is evidence that there is a higher incidence of hypertrophic scar development in those incisions or wounds that are in areas of increased skin tension.^{63–66} Methods of reducing tension across incisions and other healing wounds have therefore been investigated as a preventative measure in scar development. In a randomized, controlled trial utilizing nonstretch adhesive microporous hypoallergenic paper tape as a method of tension reduction across surgical incisions for 12 weeks postoperatively after caesarian section, they found that the treatment group had significantly decreased scar volume and incidence of hypertrophic scar development.⁶³ This method

represents an easy, affordable, and accessible method of scar prophylaxis.

Dynamic stress shielding device. A new device that further reduces tension across a healing wound is in research and development, showing promising results. This dynamic stress-shielding device is a load bearing biopolymer device manufactured using silicone polymer sheets and pressure-sensitive adhesive secured to Teflon extension sheets. The device is placed over the incision and achieves a 20% compressive stress-shielding effect across the wound.⁶⁷ In animal studies, histologic examination of tissue after wound healing using this device demonstrated significant reduction of scar area and profibrotic markers when compared with controls, effectively recreating normal skin architecture.⁶⁷ In Phase I clinical trials utilizing human subjects with in-patient controls, stress-shielding of high-tension closure abdominoplasty incisions dramatically and significantly improved scar appearance.⁶⁷ Two randomized control trials have recently demonstrated level I evidence that this device, marketed as the embrace® Advanced Scar Therapy device, significantly improves overall scar appearance compared with within-patient controls.^{68,53}

SUMMARY

Scar management is a key component of managing both surgical and traumatic wounds in both pediatric and adult populations. Treatment of extant scars has driven decades of research and product development. Preventing scar development at the onset of wound healing, however, is the ultimate goal, and it is the subject of exciting, ongoing research and development.

An important consideration in the management of pediatric patients is the acceptability of the proposed treatment regimen to both the patient and the parent. Ideally, the treatment would be effective, fast-acting, pain free, and inconspicuous. Unfortunately, this ideal treatment does not yet exist. Therefore, thorough counseling of patients and their families on the proposed treatment plan for a given scar must address reasonable patient expectations at the outset of the treatment, and should be a continuing discussion throughout the course of treatment. This should reduce patient and parent anxiety and frustration with the therapy, and prevent undue interruptions in treatment delivery. Ideally, future research that addresses pediatric-specific scar pathology and treatment methods will also aid in delivering effective, efficient, and comfortable pediatric scar management. Specifically,

TAKE-HOME MESSAGES

- Scars can create a substantial psychological, aesthetic, and/or functional burden on the pediatric patient.
- No currently available scar therapy is universally successful.
- The treatment of scars with current individual or combination therapy can improve the appearance of scars.
- It is important to develop a treatment plan that is acceptable to the physician, parents, and child.
- The majority of research in scar therapy has been performed in adults and has then been extrapolated to the pediatric population.
- Focused research on the treatment of pediatric scar therapy should be conducted.

research into treatments that focus on noninvasive, painless interventions would be most beneficial to the treatment of scars in the pediatric population.

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Abbreviations and Acronyms

BTA = botulinum toxin A
 cw-CO₂ = continual-wave CO₂
 Er:YAG = erbium:yttrium-aluminum-garnet
 Gy = Gray
 ISPeW = International Society for Pediatric Wound Care
 MMP-13 = matrix metalloproteinase-13
 PDL = pulsed dye laser
 TGF- β 1 = transforming growth factor-beta 1