PREVENTION AND TREATMENT OF EXCESSIVE DERMAL SCARRING

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Today, wound management to avoid excessive scar formation is increasingly important, especially in populations with Fitzpatrick 3 or higher skin pigmentation. Medical science and industrial development are devoting more effort toward understanding and offering better therapy to control scars. However, advances in scar management have been hampered by the confusing or ambiguous terminology. There is no consensus on what amount of post-traumatic skin scar formation is "normal" and what should be considered "hypertrophic". In the World Health Organization's ICD-9, there is no diagnostic code for hypertrophic scar—only keloid is listed.[1] Yet, the medical and scientific literature distinguishes them as different conditions. Our experience suggests that the diagnosis of keloid disease is greatly over-rendered. For black patients, an elevated scar seems, by default, diagnosed as keloid by most. This confusion results in inappropriate management of scar formation, and occasionally contributes to decision making related to elective or cosmetic surgery. Given that patients are expecting better outcomes from wound care today than in the past, this review article attempts to capture the essential biological factors related to wound scar production and discusses treatment options and indications used by the authors. (*J Natl Med Assoc.* 2004;96:108–116.)

Key words: hypertrophic scar ♦ keloid ♦ management ♦ anti-inflammatory

TERMINOLOGY

In the medical literature, hypertrophic scar is generally described as an overgrowth of scar tissue that remains within the boundaries of a wound (Figure 1).[2] The wound boundary grows wider as more scar tissue forms. Currently, no objective diagnostic criteria have been formulated to indicate when a scar can be considered hypertrophic. Keloid scars are densely collageneous, nonencapsulated, benign connective tissue neoplasms (Figure 2).[3] The size and shape of a keloid scar have little correlation to the extent of the skin wound. Large, disfiguring tumors can often result from minimal skin trauma. Keloid scars, unlike hypertrophic scars, have a genetic etiology.

A commonly taught but confusing concept is that keloids can be distinguished from hypertrophic scars by extension of the scar beyond the wound border. This concept, *per se*, implies that a scar starts out as a hypertrophic scar and later becomes a keloid when it has exceeded some vaguely defined wound boundary. Such a classification scheme sets the stage for confusion, particularly when one of the disorders is classified as a heritable disease. Scientists investigating pathologic scarring suggest that there are significant phenotypic differences between hypertrophic and keloid scars which may not be clinically obvious until they invade surrounding tissues.[4] Therefore, while keloid scars are by definition hypertrophic, only a small percentage of large scars can be truly classified as keloid.

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WOUND-HEALING BACKGROUND

In order to discuss hypertrophic and keloid scar pathogenesis and treatment, a review of the pertinent aspects of wound-healing is essential. Wound-healing is a very complex process that is tightly regulated to achieve wound repair. The process can be categorized into three distinct phases that have very different objectives: inflammation, proliferation, and maturation. Following the initial tissue injury, inflammatory mediators, known as cytokines, are released from the injured tissue cells and wound blood clot, and thereafter initiate the inflammatory phase.[5] The amount of blood released, the extent of devitalized tissue, and the bacterial content largely control the intensity of the inflammatory process. The length of time before wound closure is a critical factor of wound inflammation, as the wound does not become sterile until it regains an epithelium.[6]

If the wound-healing process is uncomplicated, the proliferation stage (also called "transitional repair stage") begins several days after the injury.[7] Platelet degranulation activates the coagulation cascade, and the resultant fibrin clot serves as a scaffold for the proliferation phase of wound-healing.[5] During the proliferative phase, the number and density of fibroblasts in the extracellular matrix increase, and the fibroblasts synthesize tissue components, such as proteoglycans, fibronectin, and collagen. New vessels and epithelium are formed as rapidly as possible to maximize the tissue-replacement dynamics. All wound cells are maximally active and are sensitive to factors that regulate cell proliferation and protein biosynthesis. As the cells proliferate, metalloproteases are simultaneously released into the extracellular fluid to activate a matrix breakdown process. The balance between tissue degradation and biosynthesis permits remodeling of the provisional tissue and also determines the net amount of scar tissue produced.

When enough provisional tissue is generated, a turn-off signal is received that initiates the final stage of wound-healing, the maturation stage. This phase is characterized by cellular apoptosis and a shift in balance from scar remodeling toward scar degradation.[8,9] The process is accompanied by extracellular matrix reorganization and reduction. Metalloproteases synthesized during the proliferation stage continue to break down the extracellular matrix at a rate largely determined by physical and biochemical factors in the matrix.[10] The amount of extracellular matrix biosynthesis is controlled by need for tissue strength and other operational parameters. Mechanical stress is an important contributory parameter in net scar production.

The most important known determinates of scar production are the extent and duration of inflammation, the magnitude of mechanical tension acting on the scar, and the genetic phenotype of the individual. Although other factors may be important—and some are yet unknown—scar management fundamentally based on these three critical parameters can be effective in limiting unnecessary scar formation in most cases.

PATHOLOGICAL SCAR

Hypertrophic Scars

Several epigenetic causes for hypertrophic scarring have been identified. Basically, factors that increase or prolong wound inflammation or wound tension predispose to hypertrophic scar formation. Such factors include wound infection, prolonged healing by secondary intention, or immunologically foreign material present in the wound. Hypertrophic scars begin as the result of an injury to the deep dermis. They are especially pronounced in wounds that have a prolongation of the inflammatory and proliferative phases of wound-healing.[7] The incidence of hypertrophic scars following surgery is about 40–70%, whereas it is higher (up to 91%) following burn injury.[6] Several reports conclude that there is a substantially increased risk for hypertrophic scarring in burn wounds that take longer than 21 days to heal.[6]

Hypertrophic scarring also occurs as the result of dynamic mechanical skin tension acting on the healing wound.[11] As a result of mechanical tension, scars located on certain areas of the body (e.g. sternum, deltoid, and upper back) are frequently hypertrophic, the typical appearance of which can be seen in Figure 1. This anatomic dependency seems to correlate with patterns of skin tension.[12] The natural history of hypertrophic scars is that they regress with time after injury, leaving behind, however, an unsightly wide gap of thinned dermis between wound edges.

A familial pattern in hypertrophic scarring is not described, however populations with higher skin melanin content are known to have a higher incidence of hypertrophic scars. These populations include people of African, Asian, and Hispanic decent.[13] Hormonal influences are also known to be a factor, with hypertrophic scarring often initiated

at the start of puberty or during pregnancy. Scar tissue cells are sensitive to the influences of the same growth factors that drive normal tissue growth and development. Schierle et al. report an increase in testosterone receptors in hypertrophic scars,[14] which may contribute to the formation of these scars during the adolescence.

Keloid Scar

Although the diagnosis of keloid scar is often inappropriately applied to hypertrophic scars, the two lesions can be differentiated at several levels. Unlike hypertrophic scars, the natural history of keloid scars is that they do not regress with time following injury. Keloid tumors grow to reach a certain size and may remain that size indefinitely. Patients with keloid scars also have an associated strong family history of keloids; both autosomal dominant and autosomal recessive modes of transmission have been reported. Castagnoli et al. reported an association between keloid occurrence and HLA-BW16, BW 21, and BW35.[15] The bulk of available evidence suggests that keloid scarring is a genetic anomaly.

The genetic basis for this disease is evidenced by the aberrant behavior of fibroblasts cells explanted from scar tissue. Several investigators have demonstrated that the keloid fibroblasts exhibit abnormal regulation of apoptosis.[8,17] It has also been reported that keloid fibroblasts *in vitro* produce abnormally high levels of collagen, fibronectin, and proteoglycans, and display atypical responses to regulation by metabolic modulators, such as growth factors and hydrocortisone.[9] McCauley et al. also reported increased serum levels of inflammatory cytokines in keloid patients.[16] Histologically, collagen bundles are thicker and more abundant in keloid scars and form acellular node-like structures in the deep dermis.[18] Several recent reports indicate that there is a persistence of inflammatory cells in keloid scars beyond that found in normal scars.[19]

In addition to the possible genetic factors, keloid fibroblasts are also quite sensitive to epigenetic factors that modulate gene expression.[20] Strong relations exist between keloid formation and age and sex hormones, with younger people being more vulnerable.[9] Keloids have been noted to enlarge during pregnancy and regress at the end of pregnancy or following menopause.[21]

Clinical Management

The first consideration in discussion of scar treatment is prevention. In the surgical setting, events occurring during the management of the open wound are important. Careful and meticulous handling of tissues, evacuation of blood from the wound, accurate wound edge alignment during closure, as well as precise suture placement, will reduce inflammation and, consequently, scarring. The choice of suture material is important because some sutures trigger more immune reaction than others. Monofilament absorbable synthetic biopolymers produce the least reaction.[22] Minimizing tension acting on the wound by aligning the incision parallel with the natural skin lines (when possible) or use of local flaps will also help to reduce the incidence of postsurgical hypertrophic scars.

Over the past two decades, a few fundamentally new therapeutic approaches to scar management have been reported. These new techniques have added substantially to existing therapeutic approaches and continue to enhance them. In the following paragraphs, we will attempt to briefly summarize some of these new concepts.

Inhibition of Scar Growth

Anti-Inflammatory Agents: The inhibition of extracellular matrix and inflammatory protein production by corticosteroids is one of the most well-established approaches to scar management.[20] At therapeutic concentrations, the multiple effects of corticosteroids on scars include inhibition of collagen and other extracellular matrix protein synthesis, decreased cytokine production, and inhibition of neovascularization. As corticosteroids decrease new protein synthesis, the balance between matrix synthesis and degradation is disrupted, allowing previously synthesized collagenase and other metalloproteases to decrease the amount of scar tissue.

Long-acting synthetic glucocorticoids—such as triamcinolone—are most commonly used for treatment of hypertrophic and keloid scars. Synthetic glucocorticoids, applied topically, are weakly soluble in water but well absorbed in the epidermis. With time, they slowly diffuse into the scar. Alternatively, solutions of triamcinolone can be injected in 10–40 mg/mL concentrations.[2,23] Both methods of delivery are effective in the majority of noninfected scars that exhibit symptoms such as pain and pruritis.[24] However, the morbidity of repeated injections on a monthly basis, fat atrophy, and the depig-

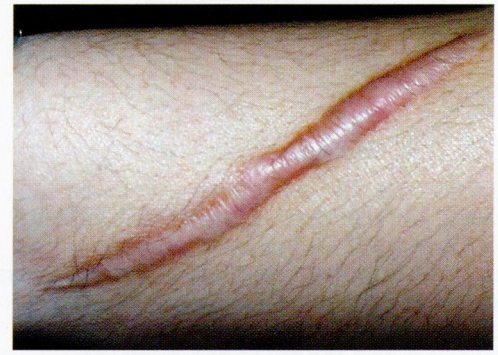
mentation of skin are major drawbacks to these treatments. Steroids are not often useful for treatment of older scars that are less metabolically active and also are not routinely used as a scar preventative immediately after wound closure because of concern about wound infection or dehiscence.

The inflammatory response can be regulated at several different physiological levels before, during, and after inflammatory gene expression. Before gene expression are transcription factors, such as NF-kB (Nuclear Factor-kB), that are activated by cell injury. After gene expression are inducible enzymes, such as cyclooxygenases, which produce cytokines that orchestrate multicellular responses. Three common ways to control inflammation include inhibition of the NF-kB pathways that signal inflammatory gene induction that regulates inflammation, inhibition of prostaglandin production via cyclooxygenase (COX) regulation, and inhibition of histamine synthesis. The most widely used anti-inflammatory agents belong to the broad category of nonsteroidal anti-inflammatory drugs (NSAIDs). They inhibit either the NF-kB pathway or COX activity, or both. It is noteworthy that corticosteroids exert a broad anti-inflammatory effect through inhibition of multiple inflammation transcription factors NF-kB, AP-1 (activator protein-1), and NF-AT (nuclear factor of activated T lymphocytes).[25]

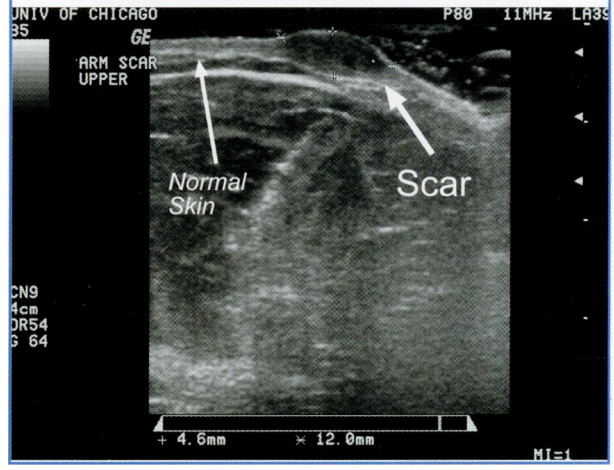
NF-kB is a rapid-response transcription factor that is involved in the cellular stress response.[26] NF-kB is involved in the up-regulation of cell membrane receptors to inflammatory peptides. It is also involved in the production of cytokines, chemokines, and growth factors. NF-kB activation can be inhibited by several different agents. These agents include cyclosporine, tacrolimus, antioxidants, and salicylates (including aspirin). Salicylic acid indirectly inhibits NF-kB expression by blocking the enzymes which lead to dissociation of IkB (the inactivator of NF-kB) from the NF-kB complex in the cytoplasm. This dissociation subsequently decreases the amount of inflammation.[26] Aspirin not only inhibits the NF-kB pathway but also irreversibly inactivates both COX isoforms. Salicylates (2–5%) are commonly used to control certain causes of dermatitis and are routinely used in acne treatment products. Our experience increasingly suggests that topical application of salicylates to painful and itching scars is a practical approach to reducing inflammation. Topical aspirin should be used under a physician's guidance,

Figure 1

(a) Appearance of a hypertrophic surgical scar located on the forearm of a woman with Fitzpatrick 3 skin type at one-year post-operatively.



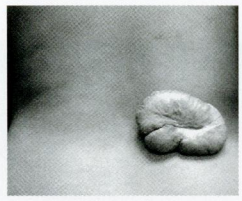
(b) High-resolution (11 MHz) ultrasound image demonstrates penetration of scar beneath skin. Ultrasound imaging is useful for measuring scar dimensions.



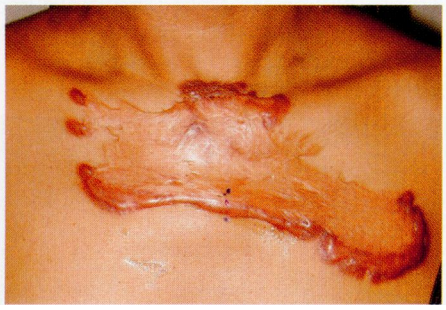
because some patients—particularly asthmatics—may develop hypersensitivity. Vitamin D3 (Dovonex®), which is also used to treat dermatitis, is another inhibitor of NF-kB. The action of Vitamin D3 is due to its affinity for the DNA promoter regions that transduce the NF-kB dissociation signals. To date, one prospective uncontrolled study of topical salicylic acid has been reported by the senior author. Nonetheless, the number of physicians prescribing topical anti-inflammatory agents is increasing. Our personal clinical experience has been very encouraging of the effectiveness of topical 2% salicylic acid (Avosil®, Avocet Polymer Technologies, Chicago) in managing pruritic growing scars.

Figure 2

(a) Three-year-old, inflamed, and enlarging keloid scar on lower back secondary to a varicella-zoster lesion.



(b) Characteristic spreading of keloid scarring can be appreciated in this patient. Scar began with folliculitis in center of chest and spread to the lateral chest over 14 years. Scar-spreading mimics wave propagation, leaving flat disfigured skin behind the thickened and tender scar wavefront.



Prostaglandins are a group of potent hormone-like substances that mediate a wide range of physiological functions, such as control of blood pressure and contraction of smooth muscle.[27] The synthesis of prostaglandins is also central to the inflammatory response. The most common strategy for prostaglandin synthesis blockade is pharmacological inhibition of cell-membrane-bound COX.[25] COX-1 is expressed constitutively throughout the body, especially in the stomach and kidneys. COX-2, however, is expressed constitutively only in the brain and kidneys.[28] COX-2 syntheis is highly inducible by activation of NF-kB, which occurs at sites of injury or infection and plays an important role in fibrosis. The adverse side effects of COX inhibition are minimized by the use of specific COX-2 inhibitors, making them agents of choice for prolonged usage. The therapeutic value of these agents in rheumatologic disease is well established, but their potential value in the management of hypertrophic scarring has been a more recent consideration. Our reported experience suggests that COX-2 inhibitors reduce symptoms of pruritus and may induce scar maturation and involution.[29] Some popular topical consumer scar treatment products derive from onion extract (i.e., Mederma®, Merz Pharmaceuticals) which has anti-inflammatory properties.

Antihistamines are commonly used to control symptoms of scar pruritus, but they also seem to exert an antifibrotic effect on scars.[30] Antihistamines, particularly the H1 blockers, inhibit the inflammatory response, resulting in reduced scar formation and increased comfort. The inflamed scar is scratched less, which will most likely reduce the scar growth rate. Antihistamines are also well known to inhibit collagen synthesis.[31] Diphenhydramine (Benadryl®, Pfizer) and hydroxazine (Atarax®, Pfizer) are the most commonly used antihistamines for scar management. In the past few years, we have preferred the use of long-acting, nondrowsy formulations, such as loratadine (Claritin®, Schering) or fexofenadine (Allegra®, Aventis), which have the advantages of sustained action and fewer CNS side effects.

Inhibitors of Gene Transcription: The antimetabolites mitomycin-c and 5-fluorouracil inhibit proliferation of cells by blocking DNA synthesis and transcription through competitive inhibition of thymidylate synthesis.[32] A single application in the first few days after wound closure seems to be effective. Antimetabolite-induced apoptosis has also been demonstrated in Tenon's capsule fibroblasts.[33] Thus, these agents are likely to be helpful in scar control.

Growth Factor Inhibition: The Transforming Growth Factor Beta (TGF-b) family of proteins is centrally involved in regulating wound-healing.[9,18] TGF-b synthesis and release is activated by injury, and along with Platelet Derived Growth Factor (PDGF), it has a central and critical role in induction of wound-healing. Binding of TGF-b to its receptor on fibroblasts causes fibroblast proliferation, extracellular matrix structural protein synthesis, and TGF-b synthesis. Mannose-6-phosphate and several other disaccharides sterically limit TGF-b binding to its receptor and limit scar formation in experimental wound-healing models.[34]

Accelerators of Scar Degradation Rate

While anti-inflammatory agents and growth factor inhibitors can limit scar production, strategies to accelerate scar tissue degradation are also very useful. This approach may be the best for management of older hypertrophic scars and older keloids. The

rate of tissue breakdown can be increased by both pharmacologic and physicochemical means.

Occlusive Dressings: After elastic pressure wrap dressings of healing burn scars were observed by Larson et al.[35] to be effective in the reduction of scar hypertrophy, 20–204 mm Hg pressure garments became the mainstay of scar prevention. The mechanism of action of pressure dressings is unknown, because they remain effective even when they lose elasticity and pressure after several weeks of daily use. Measurements show a decrease in wound metabolism with an increase in collagenase activity.[36] Drawbacks to their use are primarily related to thermal insulation and movement restriction.

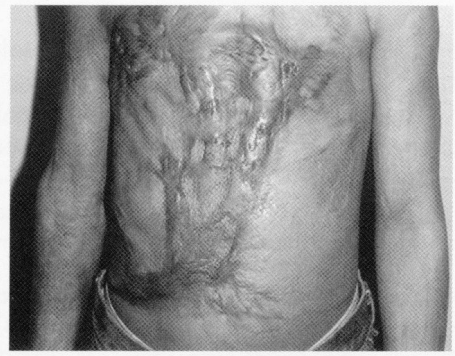
Both hydrogel and silicone gel sheeting have also been used to control scar formation (Figure 3).[37-40] Like elastic garments, the mechanism of action has not been clearly defined. Several putative mechanisms have been reported in the literature, including: induction of scar hypoxia, increased hydration of the epidermis covering the scar, and increased scar temperature.[41,42] The effect does not depend on the composition of the gel sheeting used. It is clear, however, that release of silicone into the scar is not the mode of action. Several reports have shown that hydrogel sheeting is equally effective as silicone and has fewer adverse side-effects.[43,44] Hydrogel sheeting has recently been approved by the FDA as substantially equivalent to silicone for treatment of hypertrophic scars. Hydrogels have the added advantage of use as a hydration vehicle, as well as a higher heat capacity for maintaining a continuous elevation of scar temperature.[39]

Inducers of Scar Degradation

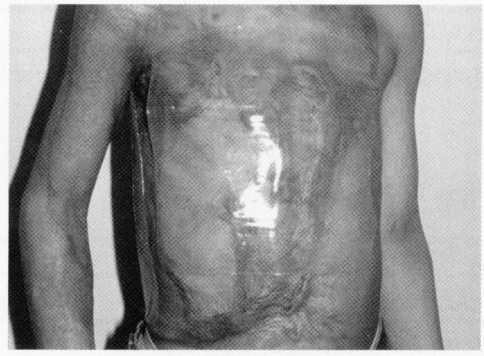
Calcium Antagonists: Many organic calcium channel blockers (i.e., verapamil) induce collagenase production and scar tissue degradation. They induce changes in fibroblast gene expression, resulting in decreased collagen synthesis and increased collagenase production. These effects appear to be mediated by interruption of the basic cellular G-protein signal transduction pathway that is critical to regulation of fibroblast behavior.[45] This pathway can be interrupted at multiple points by a wide range of commonly used drugs.[46] Verapamil, injected into the lesion, has been shown to induce scar degradation in the skin, fascia, and periocular tissue.[47] Our personal experience is that use of 4–5% verapamil in a cream base applied topically on the scar avoids rebound scarring from the trauma of intralesional injections.

Figure 3
Response to hydrogel application on a hypertrophic burn scar over 12 weeks of usage. At the time of hydrogel (Avogel) application the patient was eight months after grafting.

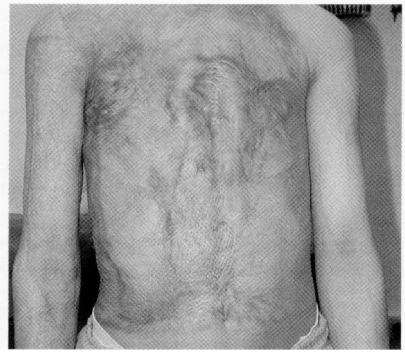
(a) Hypertrophic, inflamed skin graft scars before hydrogel therapy.



(b) Placement of hydrogel sheet. The sheet was held in place with elastic netting 10–14 hours per day.



(c) Appearance of the scar at 12 weeks after hydrogel sheet therapy, showing considerable improvement in scar size.



If injection is necessary, then alternating verapamil with cortisone injections at monthly intervals seems to generate an effective yet less robust response.

Additional agents which may induce scar degradation include other calcium channel blockers, calmodulin inhibitors (i.e., trifluoperazine), and specific protein kinase C (PKC) inhibitors (i.e., tamoxifen). These agents hold promise as treatment for older, noninflamed scars that are no longer actively remodeling.

Apoptosis Inducers: The density of keloid scar fibroblasts does not decrease as the scar ages. Instead, keloids continue to produce thick collagen bundles in a nodular array. They also produce high levels of the proteolytic enzyme Caspase-3.[8] Sayah et al. proposed that the down-regulation of apoptosis-related genes in fibroblasts could alter fibroblast phenotype, leading to increased scar tissue production.[17] A pharmacologic agent that could block the expression and ultimate production of Caspase-3 could be very valuable in the treatment of hypertrophic and keloid scars.

Low-dose ionizing radiation is a well established method of therapy for hypertrophic scarring and keloids.[48,49] The primary mechanism of radiation-induced scar control seems to be apoptosis of proliferating cells in the scar tissue.[50] Low-dose ionizing radiation is most often reserved as the method of last

Figure 4. Overview of Scar Management Protocol at University of Chicago Scar Clinic

Scar Type:	**Immature Hypertrophic (0–6 months)**	**Mature Hypertrophic (>6 months)**	**Ear Keloid Fibroma**	**Widespread Keloid Disease**
Step 1: Scar evaluation and classification				
Document scar symptoms	Scar Symptom Survey			
Measurement	Baseline ultrasound of reference point; photographs			
Step II: Control inflammation				
Anti-inflammatory drug	Topical 2% salicylic acid		COX-2 inhibitor (p.o.). If pruritus persists, then add nonsedating antihistamines	COX-2 inhibitor (p.o.); If pruritus persists, then add topical 2% salicylic acid and/or nonsedating antihistamines
Step III: Accelerate scar maturation				
Occlusive barrier	Hydrogel sheeting		Hydrogel sheeting as appropriate	
Step IV: Stimulate scar degradation				
Calcium antagonist	Usually unnecessary		Topical 7% verapamil (cream base) q 24 hs	
Step V: Evaluate progress				
	Evaluate scar and symptoms q four-to-six weeks; follow progress with survey, ultrasound, photos; adjust treatment as necessary			
Step VI: Surgery and other treatments				
Surgery	Surgical excision, if necessary, to accelerate therapeutic response surgery requires that scar symptoms should be under good control			May also consider alternative therapies (radiotherapy, cryotherapy)
Step VII: Postsurgical follow-up and additional therapy				
Prevention of recurrence	Continue anti-inflammatory and hydrogel treatment strategy after therapeutic response for four-to-six months. Follow up q six- to12 weeks			

resort for the treatment of intractable keloid scars. This therapy utilizes 15–20 Gy of ortho-voltage radiation divided into five to six treatments. Although radiation therapy alone is not adequate, if used in conjunction with surgical intervention, reduction in recurrence may reach 25%, compared with a recurrence rate of up to 80% with surgery alone.

Surgical Revision: The most common indications for surgical removal of scars are the following: large scars that are unlikely to be completely managed by medical therapy in a reasonable timeframe, scars that harbor painful furuncles, and scar contractures that hamper musculoskeletal function.[51] Although the outcome of surgery may be desirable in the short postoperative term, surgical revision of hypertrophic or keloid scars is followed by a high recurrence rate.[2,3] Adjunctive measures to reduce inflammation, skin tension, and other factors are essential to reduce recurrence. Our observations indicate that most patients with scars large enough to require surgical excision require both systemic COX-2 inhibitors and long-acting H1 antihistamines to induce scar degradation and reduce recurrence. The protocol for patients that require elective surgical excision is to identify effective scar control medications beforehand, then to restart the medications immediately following surgery. Gentle surgical technique is also critically important, because inflamed scar tissue produces a tremendous scar response to trauma. The use of lasers and other burning techniques for scar removal is very controversial.

SUMMARY

Despite recent scientific progress, scar-related disfigurement and disability remain major ongoing medical problems. Stripped of the conflicting and confusing terminology, hypertrophic and keloid scarring can be essentially reduced to inflammation-mediated dermal fibrosis. This suggests that there is much insight into effective management that can be gleaned from the medical literature pertaining to dermatological and rheumatologic conditions which also have a large inflammatory gene expression component.

With these concepts in mind, the authors have designed several scar management protocols which are under clinical evaluation. Under these protocols, summarized in Figure 4, patients with scars that are actively enlarging or prurtic are treated with either topical salicylates and oral COX-2 medications to control the scar inflammation. The oral COX-2 inhibitors are reserved for patients with scars thicker than 2 centimeters or whose widespread scarring is such as that seen in keloid disease. The use of topical verapamil (5–10%) has shown great promise in inducing degradation of older inactive scars and reduced the need for surgical intervention. Transepidermal delivery of these topical agents has been enhanced by the application of an occlusive barrier, such as hydrogel sheeting (Avogel®, Avocet Polymer Technologies). Our stratified approach to scar management has resulted in the ability to effectively treat scar conditions that have been refractory to conventional therapy. We hope that this experience will lead to more-effective therapeutic options for these patients.

In this article, we have attempted to briefly summarize and place into a conceptual framework the various existing and emerging therapies for hypertrophic scar disorders. We hope that this review will encourage development and consistent use of less ambiguous terminology and more effective therapeutic strategies in the future.

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