Vehicles and Formulas:

Hypertrophic Scars and Keloids Review

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Scars come in a variety of shapes and sizes. Ideally, if a scar does form after the wound healing process a flat and thin scar would form, often called a normotrophic scar. Unfortunately, during the wound healing process irregular collaged deposition can occur leading to excessive scar tissue in the form of hypertrophic and keloid scars. Hypertrophic scars and keloids are marked by raised and red skin. Hypertrophic scars typically arise within four to eight weeks of wound closure and continue to develop over a period of months, they typically present within or just around the location of the original wound. Hypertrophic scars may also present with tightening skin or scar contractures that could potentially limit mobility depending on the area of the scar. Keloid scars may arise months to years after original injuries and may grow beyond the original borders of the wound. Keloids are more likely to occur on the upper torso, specifically the chest, shoulder, upper back, back of the neck, or earlobes.[1]

The risk of hypertrophic or keloid scars can be reduced with certain wound care techniques. One review of the use of silicone gel and silicone sheeting for the management of wounds found that studies suggest the use of silicone gel products can reduce scaring as well as scar thickness and color.[2] Some sources suggest that silicone can help to decrease scar formation by decreasing trans-epidermal water loss and maintaining optimal moisture levels. Some experts recommend starting silicone therapy when wound epithelialization is reached, approximately 2 weeks after wound closure. Silicone gels may be applied on the area, extending approximately 1-2cm beyond scar margins. When used alone, silicone gels are often applied twice daily, though, if silicon treatment is combined with another active ingredient, the rate of application may be impacted. Treatment may be continued up to 6 months to prevent reoccurences.[3]

There is some debate about the use of silicon sheets as compared to silicone gels. Some trials suggest similar benefit with both approaches. One study that had patients apply silicone gel to half of their wounds and silicone sheets to the other half found no statistical difference between groups using the Vancouver Scar Scale or Visual Analogue Scale for evaluation. Silicone gel may have been superior to the sheet in terms of itching, though, the authors remarked that the difference between groups was small such that clinical significance was difficult to discern.[4] Another meta-analysis of the use of silicone gel generally found that silicone gels significantly reduced pigmentation, height, and pliability scores for postoperative scars as compared to either placebo or no treatment depending on the study.[5]

In addition to silicone gel as a vehicle, some active pharmaceutical ingredients (APIs) have been studied for utility for scarring as well. Retinoids have been evaluated for potential use for preventing hypertrophic scars and keloids. Though there may be a variety of mechanisms at play, the impact of tretinoin and retinoids generally on scars may be related to enhancing skin cell turnover and improving the color and elasticity of the scarred skin. One study on topical tretinoin 0.05% for one year on the skin of patients who had suffered partial thickness burns found that tretinoin significantly lowered skin resistance and improved elasticity. The study did

not note significant differences in density of collagen fibers. Patients who used tretinoin reported better quality of life associated with treatment.[6] Another comparison trial evaluated silicone gel vs tretinoin cream vs placebo applied twice daily. The study found that both silicone gel and tretinoin worked to prevent hypertrophic scars and keloids and to improve existing scars after surgery as compared to placebo treatment. The difference between silicone gel and tretinoin treatment didn't reach the level of statistical significance.[7] Other older studies, such as one that looked at 0.05% tretinoin applied topically for 12 weeks, found significant improvement in scar size and weight after 12 weeks of treatment.[8]

Tretinoin has also been studied in combination with alpha hydroxy acid glycolic acid, a keratolytic agent. One study of tretinoin 0.01-0.05% with glycolic acid 5-7% over a 3 month period found the combination to improve skin appearance and elasticity in patients with burn scars, allowing those who had received burns to the face greater mouth opening range compared to the controlled group.[9] Glycolic acid has also been evaluated as a solo agent either in peel form or with topical daily use for atrophic acne scars. One single, blind, placebo-controlled trial compared every other week glycolic acid peels (20, 35, 50, and 70% concentrations) to glycolic acid 15% cream once or twice daily use over a 24-week period to a control group. The study concluded that high concentration (70%) glycolic acid peels were less well tolerated than daily glycolic acid but produced superior reduction in scar reduction than lower peel concentrations, daily glycolic acid cream, or placebo.[10]

Captopril is another potential candidate for topical scar treatment. Hypertension-induced endothelial dysfunction is thought to be a causative factor in cutaneous fibrosis.[12] A case study of a patient with a postburn keloid scar evaluated captopril 5% applied twice daily. The study found that topical captopril reduced the height, redness, and scaling of the patient's scar, the patient's blood pressure before and after treatment was not reported, but the treatment was well tolerated.[11] Though studies in humans are limited, other animal data also supports the utility of captopril, though a study in rats found statistically significant benefit only in hypertensive rats who used captopril for scarring.[12] More data is needed to determine if captopril is effective for reduction of scarring, and if so, if this benefit is limited to hypertensive patients. Other in vitro data noted that captopril may play a role in inhibiting proliferation and collagen synthesis in keloid fibroblast cells, which could indicate hypothetical benefit outside of hypertensive patients.[13]

Verapamil HCl is another active ingredient typically used for hypertension that has been studied for potential utility against scaring. The proposed mechanism for verapamil is thought to be due to its ability to inhibit collagen production. Verapamil HCl may also inhibit inflammation via decreasing neutrophil activity.[14] Currently, most of the data on verapamil HCl for scarring focusses on intralesional use. For example, one study of combined triamcinolone 40mg/mL and verapamil HCl 2.5mg/mL injected into scars found treatment to significantly improve Patient and Observer Scar Assessment Scale score.[14] Verapamil HCl has been studied topically in a more limited capacity for scaring. One animal study in rabbits applied verapamil HCl 0.25mg, 2.5mg, or 25mg/g in a silicone gel to scars. The verapamil HCl 2.5mg/g group had a lower median scar elevation index as compared to silicone gel alone.[15] A separate study in rabbits looked at 0.1, 1, and 10mg/g verapamil HCl in silicone gels. The study found lower collagen expression in the 1mg/g and 10mg/g groups, but not in the lower concentration group. The verapamil HCl added groups did all show improved scar elevation index as compared to silicone gel alone.[16] Further dose finding studies to identify the most helpful concentration of verapamil HCl are needed.

Topical losartan is another candidate for potential use for the management of hypertrophic scars and keloids. Losartan is hypothesized to inhibit fibrosis and reduce the expression of collagen via inhibition of angiotensin II. A pilot study had patients apply 5% losartan ointment or placebo twice daily for three months. Vancouver Scar Scale score was significantly improved in the losartan group and vascularity and pliability were noted to be

reduced by losartan treatment.[18] Another study of losartan 5% ointment applied twice daily in patients after reconstructive surgery corroborated the previous study's findings, noting improvements in height, pliability, and vascularity with losartan treatment as compared to placebo.[17] Another study evaluated lower concentrations. An animal study comparing losartan 0.2% and urea cream, ramipril 0.1% cream, and a positive control test with triamcinolone acetonide urea cream compared to a negative control group found that the treatment groups had less active fibroblasts and more regular collagen fibers than the negative control group.[19] Enalapril 1% applied to wounds has also been noted in small animal studies to reduce the incidence of hypertrophic scarring. More data is needed comparing various ACE, ARB, and calcium channel blockers for topical use for scarring and evaluating appropriate strengths for topical use, but data thus far on safety and efficacy is promising.[21]

Steroids have also been studied, mainly for intralesional use, for management of hypertrophic scars and keloids. In addition to improving the appearance of scars, steroids may also improve scar related itching/pruritus. Triamcinolone acetonide specifically at 20mg and 40mg/mL either on its own or in combination with 5-fluorouracil has been found to reduce scar height and improve vascularity and pigmentation. However, compared to other treatments for scarring, such as verapamil HCl or combination 5-fluorouracil and triamcinolone acetonide, triamcinolone acetonide was also more likely to cause skin atrophy or telangiectasia.[20] Despite existing data for intralesional use, studies have yet to evaluate topical triamcinolone acetonide or corticosteroids for benefit for hypertrophic scars or keloids.

Chemotherapeutic agents are also of interest for the management of hypertrophic scars and keloids. In addition to data evaluating 5-fluorouracil in combination with triamcinolone acetonide, it has also been evaluated on its own for use against scars. 5-Fluorouracil is thought to treat scars via induction of apoptosis, potentially targeting fibroblasts in scar tissue and product apoptosis in these cells, however, data on 5-fluorouracil is mainly on intralesional therapies at this time. Other chemotherapeutic agents such as tamoxifen have been evaluated as well. Tamoxifen may also play a role in mitigation of scars and keloids. Tamoxifen is thought to inhibit fibroblast proliferation and collagen production. One animal study of tamoxifen 2% ointment applied twice daily for 8 weeks found increased angiogenesis and decreased fibrotic tissue thickness.[22,23]

Statins have also been studied in a limited capacity for topical use for scaring in animal models. Simvastatin was found to induce the apoptosis of fibroblasts and decrease type I collagen. A study of topical simvastatin 10% was found to significantly reduce scar hypertrophy compared to placebo, however, simvastatin at a lower 2% strength did not have the same effect.[22.24] Another study of simvastatin 6.5% and pravastatin 6.5% topical in 'liposomal' preparations have also demonstrated benefit for reduction of collagen and decreasing scar elevation index among other markers in a rabbit ear model.[27] Though improvement of scarring was noted in these studies, treatment with topical simvastatin also induced topical adverse effects such as scaling and erythema. Limited evidence suggests that co-application with 2% cholesterol reduced these adverse events.[25]

Agents that modify immune response have also been evaluated including tacrolimus and imiquimod. Tacrolimus has been found to inhibit proliferation and collagen production. Tacrolimus has been studied both intralesionally and topically. A study of tacrolimus 0.03% or 0.1% ointment applied to wounds was found to decrease inflammation and other changes associated with scar formation in animal models. Evidence on imiquimod is mixed, but topical imiquimod 5% applied once daily at bedtime over an 8-week period has been noted to prevent the recurrence of keloids after surgical excision of keloids.[21,26]

Topical treatment of scars and keloids can be a challenge. Prevention with appropriate wound care is key. For existing scars and keloids topical management with retinoids, calcium channel blockers, and active ingredients

that act on the renin angiotensin systems (such as angiotensin receptor blockers or angiotensin-converting-enzyme inhibitors) seem especially promising. Topical treatments for managing hypertrophic scars and keloids are often evaluated over months, with even the shorter studies looking at 8-week treatment periods, which makes setting patient expectations key for treatment success.

Vehicle	Water Activity	Utility for Hyperpigmentation Formulas
Nourisil	<0.6	Nourisil is an anhydrous silicone base with a smooth skin feel. It is compatible with a wide range of solvents and APIs commonly used topically for scarring, including high concentrations of ingredients such as Verapamil HCl. Silicon-based gels have been studied for their utility for scarring and as an anhydrous base, preparations in Nourisil may receive an extended BUD per USP <795>.
Cleoderm	>0.6	A smooth white cream base containing plant-based anti-inflammatory and peptide ingredients. Cleoderm has been demonstrated to be noncomedogenic in clinical testing, making it a potential option for acne scars or hypertrophic or keloid scars located on or near the face.
Versatile	>0.6	A smooth, white, aqueous cream base with a high API load tolerance and vanishing properties that make it cosmetically elegant. This vehicle is robust enough to tolerate high loads of active ingredients and those commonly used for scarring such as Verapamil HCl.

Formula ID	Formula Name
FA-23179	Tretinoin 0.05% - Vitamin E 1% Anhydrous Gel (Nourisil)
FA-22857	Adapalene 0.3% - Vitamin E 1% Anhydrous Gel (Nourisil)
FA-22852	Captopril 5% Anhydrous Gel (Nourisil)
FA-22512	Tretinoin 0.05% - Triamcinolone Acetonide 0.05% Gel (Nourisil™)
FA-22725	Imiquimod 5% - Triamcinolone Acetonide 0.1% Anhydrous Gel (Nourisil)
FA-24147	Verapamil HCl 1% Anhydrous Gel (Nourisil)
FA-24150	Verapamil HCl 1%, Triamcinolone Acetonide 0.1% Anhydrous Gel (Nourisil)

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