General Overview about Management of Keloid and hypertrophic scars

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Abstract

Keloid scar formation arises from a disorganized fibroproliferative collagen response that extends beyond the original wound margins because of excessive production of extracellular matrix (ECM). Despite treatment options for keloid scars including medical and surgical therapies, such as intralesional steroid injection and surgical excision, the recurrence rate remains high. Herein we consolidate recently published narrative reviews, systematic reviews, and meta-analyses to provide an overview of updated treatment recommendations for keloidal scar formation. PubMed search engine was used to access the MEDLINE database to investigate updates regarding keloid incidence and treatment. More than 100 articles were reviewed. Keloid management remains a multimodal approach. There continues to be no gold standard of treatment that provides a consistently low recurrence rate; however, the increasing number of available treatments and synergistic combinations of these treatments (i.e., laser-based devices in combination with intralesional steroids, or 5-fluorouracil (5-FU) in combination with steroid therapy) is showing favorable results. Future studies could target the efficacy of novel treatment modalities (i.e., autologous fat grafting or stem cell-based therapies) for keloid management. This review article provides updated treatment guidelines for keloids and discusses insight into management to assist patient-focused, evidence-based clinical decision making.

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Introduction

Keloid, meaning "crab's claw," was derived from Greek to describe its characteristic clinical presentation. Historically, the earliest known keloid scarring was reported around 1700 CE Egypt in the Smith Papyrus. The term was first introduced into modern medical literature in 1814. Later that century, a medical textbook published, "In regard to treatment, we are almost helpless. It is pretty certain to reappear after excision, even though the incisions be carried far into the healthy skin". Today, despite various treatment options, keloid scarring continues to escape the normal process of wound healing and remains recalcitrant. ***(1).***

Clinical characteristics:

Keloids continue to grow, unlike hypertrophic scars, which typically reach a certain size and stabilize or regress. Strict clinical and histopathological criteria have been defined to differentiate keloids from hypertrophic scars, ***(2).***

Of unknown reasons, keloids occur more frequently on the chest, shoulders, upper back, back of the neck and earlobes. In one case a massive 1.8 kg keloid has been removed from the arm at the site of vaccination. It has been intensively discussed whether keloids occur primarily in areas of high tension. This might be an oversimplification since the most commonly affected site, the earlobe, is under minimal tension and keloids appear rarely on the palms or soles where significant skin tension is to be expected ***(3)***.

Current strategies for the treatment of hypertrophic scars and keloids:

- **Intralesional corticosteroid injections and cryotherapy:**

Intralesional steroid injections have been used for the therapy of excessive scars since the mid-1960s. To date, the use of intralesional triamcinolone acetonide represents the therapy of choice for small and younger keloids as well as hypertrophic scars and effectively provides symptomatic relief by reducing pruritus ***(2).***

Effects of corticosteroids result primarily from their suppressive effects on the inflammatory process in the wound, and secondarily from reduced collagen and glycosaminoglycan synthesis, inhibition of fibroblast growth, as well as enhanced collagen and fibroblast degeneration. Three to four injections of triamcinolone acetonide (TAC) (10–40 mg/mL) every 3–4 weeks are generally sufficient, although occasionally injections continue for 6 months or more ***(4)***.

Response rates vary from 50% to 100%, and recurrence rates from 9% to 50%. Adverse events include dermal atrophy, telangiectasia, and pain at the injection site. The latter can be averted by topical anaesthesia and/or regional injections of local anaesthetic around the scars to be injected. For older hypertrophic scars and larger keloids, the combination with cryotherapy appears more effective and currently represents the most widely used modality in daily routine ***(5)***

Indeed, combination of cryotherapy with intralesional TAC injections seems to yield marked improvement of hypertrophic scars and keloids. Cryotherapy is believed to induce vascular damage that may lead to anoxia and ultimately tissue necrosis. A delay of approximately 3–4 weeks between sessions (approximately three to six sessions are needed) is usually required for postoperative healing, and commonly occurring side effects include permanent hypo- and hyper- pigmentation, blistering, and postoperative pain ***(6).***

Cryotherapy is usually performed directly before the injection of TAC, since success rates appear to be increased based on the larger amount of

TAC that can be injected into the scar due to edema formation caused by cryotherapy ***(7).***

➢ **Pressure therapy:**

Pressure therapy has gained popularity for the management of hypertrophic scars and keloids. To date, pressure garments are frequently being used for the prevention of excessive scar formation post-burn. However, their underlying mechanism of action remains poorly understood. Decreased collagen synthesis by limiting capillary perfusion and thus decreased oxygen supply to the scar tissue as well as increased apoptosis rates of fibroblasts are being discussed ***(6).***

Pressure therapy is usually performed with pressure suits or bandages, sometimes with transparent plastic masks or pressure buttons in special locations. Recommendations for the amount of pressure and the duration of the therapy are merely based on empirical observations and support continuous pressure of 15–40 mmHg for at least 23 hours per day for more than 6 months while the scar is still active. In a recent study, the use of 20– 25 mmHg was significantly superior to treatment of hypertrophic scars with 10–15 mmHg ***(4)***.

➢ **Radiotherapy:**

Superficial X-rays, electron beam and low- or high-dose-rate brachytherapy have been employed primarily as an adjunct to surgical removal of keloids, with overall good results in terms of reduced recurrence, with the exception of one report. Radiation mediates its effects through inhibition of neovascular buds and proliferating fibroblasts, resulting in decreased collagen production ***(8)***

Electron beam irradiation should be started early (24–48 hours) after keloid excision. A total dose of usually 12 Gy divided into six to ten fractions applied daily or every second day is currently recommended by dermatologists. Side effects include hypo- and hyper-pigmentation, erythema, telangiectasia, and atrophy. Since radiation represents some risk in terms of carcinogenesis, particularly in areas such as the breast or thyroid, its use should be handled with caution ***(5)***

➢ **Silicone based products:**

Silicone gel sheeting represents a well-known management for scars since its introduction in the early 1980s, and its therapeutic effect on unpleasant scars has been well studied. Current opinion suggests that normalization of transepidermal water loss is likely the underlying mechanism of silicone gel products rather than an inherent anti-scarring property of silicone ***(8)***

Silicone sheets are usually being employed 12–24 hours per day over a period of 12–24 weeks beginning 2 weeks after wounding. Currently published studies are concluding mostly positively in favour of the evaluated silicone-based therapy. A recent Cochrane review, however, determining the effectiveness of silicone gel sheeting in the treatment and prevention of keloid and hypertrophic scarring concluded that most studies are of poor quality and thus the efficacy of silicone gel sheets remains unclear ***(4)***.

<u>Fluorouracil (5-FU):</u>

5-Fluorouracil U has been successfully used for the therapy of keloids and hypertrophic scars, as demonstrated in several studies. 5-FU inhibits the proliferation of fibroblasts as a pyrimidine analogue. The response rate in keloids is an estimated 50%. So far, most studies use the high-dose version of 5-FU therapy (40–50 mg/mL) aiming to destroy the keloid ***(8)***

Other studies are supporting the combination of 5-FU and TAC. In a prospective study with a total of 69 patients, the combination of TAC (40 mg/mL) and 5-FU (50 mg/mL) (1:9) once weekly for 2 months, injected strictly intralesionally,

was shown to be superior to exclusive weekly injection of TAC 40 mg/mL ***(5)***

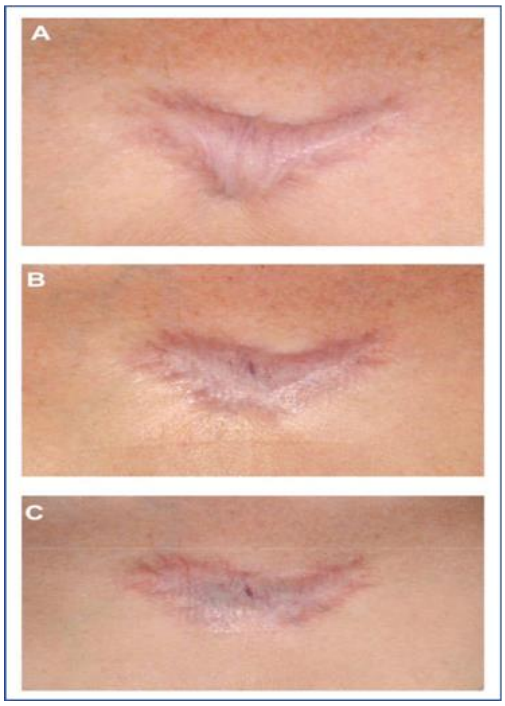

Figure (1): Patient with keloid in the presternal area resistant to cryotherapy and triamcinolone acetonide (TAC), silicone gel sheeting, surgery, and postoperative radiotherapy (recurrence) suffering from severe pruritus at baseline (A). Significant reduction of pruritus and flattening after 1 week of injection with 5-FU (50 mg/mL) and TAC (40 mg/mL), 3:1 (B). Result at 6 months after the last injection (two injections total), with no signs of recurrence, no pruritus (C).

Onion extract (extractum cepae):

Extractum cepae acts in an anti-inflammatory manner and is bactericidal. It is currently believed that the flavonoids (quercetin and kaempferol) in onion extract play the main role in reducing scar formation through inhibition of fibroblast proliferation and collagen production. Several studies suggested that these inhibitory effects may be mediated through inhibition of TGF-beta1 and -beta2 and SMAD proteins by quercetin ***(9).***

Today, an increasing body of literature is available testing the ultimate benefit of onion extract containing scar creams. Nevertheless, former clinical results are in part contradicting regarding its efficacy. However, based on recent studies, onion extract containing scar creams do significantly improve scar height and associated symptoms compared with placebo84 and appear to be effective for the prevention of unpleasant scars in patients having laser removal of tattoos as well as in combination with intralesional triamcinolone acetonide ***(6).***

Based on the published German guidelines on scarring, onion extract-containing scar creams can be considered as additional therapy for active hypertrophic scars and for post-surgical prophylaxis of excessive scarring ***(4)***.

A novel intralesional cryosurgery cryoneedle has been introduced. The probe which is inserted into the hyper- trophic scar or keloid, is connected to a canister of liquid nitrogen, which causes the cryoneedle to freeze thereby freezing the scar tissue from the inside out. An average of 51% of scar volume reduction was achieved following a single cryogenic treatment ***(8)***

Scar volume reduction of 70% for ear keloids and 60% for keloids on the upper back, shoulder, and chest was achieved following a single cryo-session, as demonstrated in a recent study. Significant alleviation of clinical symptoms was achieved. No worsening or infection of the treated scars was noticed, and only minimal hypopigmentation was evident. The non-response rate of this technique was less than 3% ***(5)***

This technology demonstrates increased efficacy compared with that obtained with contact/spray probes and may thus represent a promising alternative scar reduction strategy. Although this technology is relatively costly, it appears comparatively cost-effective, since frequently a single cryo-session is sufficient, in order to

significantly improve the hypertrophic scar or keloid. ***(2).***

Bleomycin:

Bleomycin sulphate is thought to inhibit collagen synthesis via decreased stimulation by TGF-beta1.Demonstrating significant improvement in hypertrophic scar and keloid height and pliability as well as reduction in erythema, pruritus, and pain after three to five injections (via multiple needle puncture or jet injections) of bleomycin (1.5 IU/mL) ***(4)***.

Sporadically, development of depigmentation and dermal atrophy has been noted. Due to its toxicity, clinicians are encouraged to be aware of associated potential problems. However, systemic toxic effects of intralesionally administered bleomycin appear to be rare. Bleomycin may thus represent a promising agent for the therapy of keloids and hypertrophic scars; however, further investigation and efficacy trials are necessary to include this agent in future treatment protocols ***(2).***

Interferon (IFN):

Based on the finding that IFN markedly decreases synthesis of collagen I and III, IFN has been suggested as an effective means for the improvement of excessive scars. Particularly, IFN-beta2b has been proposed to have antiproliferative properties and may improve the pathologic features of dermal fibrosis directly or by antagonizing the effects of TGF-beta and histamine **(*6).***

Intralesional injection of IFN-beta2b (1.5 million IU, given twice daily over 4 days) resulted in 50% reduction of keloid size after only 9 days and was thus more effective compared with intralesional corticosteroids. Also, hypertrophic scars injected three times weekly with IFN-beta2b demonstrated significant improvement and sustained reduced serum TGF-beta levels ***(8)***

Botulinum toxin A (BTA):

Botulinum toxin A immobilizes local muscles, reduces skin tension caused by muscle pull, and thus, decreases microtrauma and subsequent inflammation. Reduction of the tensile force during the course of cicatrisation and effective regulation of the balance between fibroblast proliferation and cellular apoptosis may represent a novel therapeutic option for the aesthetic improvement of post-surgical scars (***5)***

By injecting BTA 4–7 days prior to surgery, similar results had been noted using a slightly reduced dose regime, depending on the respective anatomic location (risk of severe asymmetry if injecting only one side of the musculus frontalis, brow ptosis) ***(5)***

Intralesional injection with BTA has been proposed for the treatment of established keloids in a prospective, uncontrolled study. BTA was injected into the lesions at 3-month intervals for a maximum of 9 months at a concentration of 35 units/mL. Total doses ranged from 70 to 140 units per session. At 1-year follow up, three of the included 12 patients demonstrated excellent, five good, and four fair results. In none of the patients did this therapy fail ***(9).***

Photodynamic therapy (PDT):

Topical PDT has been used extensively in treating superficial basal cell carcinoma, actinic keratosis, and Bowen's disease. Very recently, PDT has been suggested as a novel therapeutic approach for the treatment of keloids. The potential underlying mechanism is currently unknown. However, the photodynamic reaction generates reactive oxygen species, which in turn leads to cell apoptosis, membrane, and mitochondrial damage, and activates various signalling molecules such as tumor necrosis factor-beta ***(9).***

Photodynamic therapy has been demonstrated to reduce type I collagen synthesis and fibroblast proliferation in vitro, which may be responsible for the improvement seen clinically. which demonstrate that three treatments of PDT (37 J/cm2) at weekly intervals were effective in reducing pruritus and pain, and in increasing pliability of symptomatic keloids ***(5)***

Recombinant TGF-beta3, Justiva (avotermin):

Intradermal avotermin (recombinant, active, human TGF-beta3, Justiva) was administered in healthy subjects to both margins of 1 cm, full-thickness skin incisions, before wounding and 24 hours later and was judged to be effective by lay observers and clinicians (***9).***

Even though the investigators acknowledged their commercial interests in TGF-beta3, adherence to established standards in this translational investigation and the rigorous nature of the statistical analysis in a well powered series of studies provided strong evidence for the benefits of Justiva in this setting ***(5)***

However, Justiva failed to hit its primary and secondary endpoints in a pivotal Phase III trial. In light of that, the company regrettably concluded that the efficacy of Justiva may be insufficient to demonstrate significant benefit when tested in a broad population of scar revision patients. To date, the clinical future of recombinant TGF-beta3 remains uncertain ***(5)***

Conflict of Interest: None

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