Management of Keloids: State of the Art

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S010 -- Skin of Color

Historical Context

- Earliest recorded reference to keloids is in the Smith Papyrus (~1700 BC)
- Written in ancient Egypt; world’s oldest surviving surgical document.
- “the existence of swellings on his chest, large, spreading and hard”

Historical Context

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- Term *cheloide* first used by French dermatologist Jean-Louis-Marc Alibert in early 1800s
- Derived from the Greek *chele*, or crab’s claw, and refers to the lateral growth of the scar into unaffected skin

Keloids

- Raised scars which grow invasively beyond the boundaries of the original wound
- Cause cosmetic defects/deformities and substantial morbidity (pruritus &/or pain)
- Predilection for the chest, upper back, shoulders, and earlobes
- Higher incidence:
  - between 10 to 30 years of age
  - after puberty and during pregnancy
  - in those of African, Hispanic or Asian ancestry

Comparison of location of keloids in individuals with single site versus multiple site keloids

The Morbidity of Keloids

- Study from Turkey in which quality of life was assessed in patients with keloids/hypertrophic scars, patients with psoriasis, and sex/age-matched controls
- Used a Turkish version of the Dermatology Life Quality Index questionnaire
- Keloids/hypertrophic scars were as detrimental as psoriasis when it came to affecting patients’ quality of life

Balsi et al., J Dtsch Dermatol Ges. 2009;7:688-692

Diagnosis of Keloids

- Diagnosis often made clinically
- Punch biopsy is an option when in doubt
- Differential Diagnoses:
  - Dermatofibrosarcoma Protuberans
  - Lobomycosis
  - Rosai-Dorfman disease
  - Dermatofibroma
Treatment Options for Keloids

Surgical excision
Intralesional steroids
Silicone sheets
Intralesional 5-Fluorouracil
Intralesional bleomycin
Intralesional verapamil
Intralesional interferon
Topical imiquimod
Compression therapy
Radiation therapy
Laser therapy

No treatment to date has been 100% effective in preventing the occurrence or the recurrence of keloids

Approach to Keloid Treatment/Prevention

- Location
- Single site vs multiple sites
- Initial occurrence versus recurrence
- Family History

- Treatment of established keloids
  - cosmetic appearance

- Treatment of established keloids
  - symptomatology (pruritus, pain)

- Prevention of keloid occurrence/recurrence
Surgical Excision

- Surgical excision alone has a high recurrence rate (45-100%), with the keloid often returning larger than the original scar
- Follow-up treatment plan after surgical excision is critical
- Orient scars along relaxed skin tension lines
- Minimize amount of deep sutures
- Removal superficial sutures relatively early (7-10 days post-op)

Silicone Sheets

- FDA-approved for treatment of keloids and hypertrophic scars
- Worn over the surgical scar for 12-24h a day for several months
- Their mechanism of action is thought to be secondary to occlusion and hydration
- More effective in post-surgical setting or new hypertrophic scar than for already formed keloids
Silicone Sheets Better for Hypertrophic Scars than Keloids

- Silicone gel sheeting used in 94 patients (11-73 years of age) with abnormal scarring on the lower extremities
- Fresh and long-standing scars included in the study
- 80 patients with hypertrophic scars – 74 greatly improved, 5 somewhat improved with treatment
- 14 patients with keloids – 5 greatly improved, 5 somewhat improved with treatment


Review of Silicone Sheeting/Gel for Hypertrophic Scars and Keloids

- MEDLINE, EMBASE, CINAHL, and CENTRAL databases (1/1/1990 - 9/24/2014)
  - any controlled clinical trials comparing silicone sheeting or gel with a control group
  - Risk ratios (RR) calculated from each trial; combined using random-effects model meta-analysis
- Ten trials in 9 studies were pooled (random effect; I² = 88%)
  - significant difference between the treatment group (silicone sheets or gel) and placebo group in preventing hypertrophic scars and keloids
    (RR 0.70; 95% CI, 0.49–0.99; P = .04)
  - statistical significance in the effectiveness of silicone gel sheeting in the prevention of hypertrophic scars and keloids (RR 0.41; 95% CI, 0.24–0.72; P = .002) but not for the effectiveness of the silicone gel

Hsu et al. Wounds 2017;29(5):154-158
**Intralesional Corticosteroids**

- FDA-approved for treatment of keloids: decrease collagen formation and promote increased collagenase activity

- Triamcinolone acetonide (10-40mg/mL) injected into the surgical area immediately after keloid excision

- Injections done every 4-6 weeks to treat formed keloids -- for several treatments or until the lesion has flattened

- The main side effects are injection pain, dyspigmentation, and skin/fat atrophy

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**Some Keloids do not Respond to IL Steroids**

Correlation between responders and upregulation of glucocorticoid receptor

**Intralesional 5-Fluorouracil**

- 50 mg/mL, once monthly to three times weekly
- Useful for patients unresponsive to steroid injections
- Lesser risk for skin atrophy and telangiectasias; greater risk for hyperpigmentation and wound ulceration
- Superior results when combined with corticosteroid injections
- Combination regimen is a mixture of one part triamcinolone (40 mg/mL) to nine parts 5-fluorouracil (50 mg/mL)


**Triamcinolone vs Fluorouracil vs Both**

- 60 patients randomly allocated to three groups that received intralesional injections every 3 weeks until 24 weeks or until the keloid resolved
  - triamcinolone acetonide (TAC) in Group TAC
  - 5-fluorouracil (5FU) in Group 5FU
  - combination in Group T+F

**Results**

- improvement in terms of height, vascularity and pliability was fastest with 5FU, TAC and T+F group, respectively
- decrease in pigmentation was significantly faster with T+F
- reduction in pruritus, was significantly faster with 5FU

Triamcinolone vs Fluorouracil vs Both

Side Effects
- Telangiectasias and skin atrophy were seen most commonly in TAC group.
- Skin ulceration was a common problem in 5FU group.

Conclusions
- TAC, 5FU and their combination are all effective in keloid scars.
- A combination of TAC+5FU seems to start showing benefit faster and with lesser adverse effects when compared to individual drugs.


Syringe Preferences

- Use “lock” type syringes over “slip” type syringes to decrease the chance for backsplash.

- “Pascal’s Law”: Injecting with a syringe of smaller diameter will increase the pressure of the liquid at the tip of the needle.
Topical Skin Refrigerant Spray

- Cooling sensation decreases discomfort associated with intralesional injections
- Two-three second application (white frost appears) then immediately proceed with injection
- Beneficial when multiple keloids need to be injected

Local Anesthesia

- Anesthetize prior to treatment with 1% lidocaine with epinephrine
- Anesthetize around and deep to the keloid as if preparing for an excision
- Allows for larger bore needles; more steroid deposition, less patient morbidity
**Topical Imiquimod**

- Appropriate in post-surgical setting for keloid prevention
- May have better efficacy with shaved scars (e.g., posterior earlobe) versus excision and primary closure
- Application daily to every other day for two months, usually starting two weeks after surgery
- Side effects include hyperpigmentation, irritant contact dermatitis, erosion, and pain
- Coverage for keloids is insurance-dependent


**Intralesional Cryotherapy**

- Hand-held cryosurgical instrument
- Double lumen probe inserted intralesionally
- Direct thermal effect on the deep scar
- Softening and normalization of collagen within and surrounding the scar
- Up to 97% effective
- One treatment session
- Little downtime
- End skin surface temperature of intralesional cryotherapy is -15°C
- Melanocytes destroyed at or below -5°C
- Mostly reports treated Fitzpatrick skin types I-IV

**Intralesional Cryotherapy**


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**Compression Therapy**

- Mechanical compression has been used primarily to treat earlobe keloids, but can be used in other locations.

- After surgery, compression devices/garments are used, which are most effective if worn 24h/day for several months at a pressure level of at least 25 mmHg.

- Mechanism of action is unknown; decreased oxygen tension from occlusion of smaller blood vessels or decreased mechanical tension.
Radiation Therapy

- Often in combination with surgical excision
- Usually given within the first 2 weeks post-excision (often started within 72 hours of excision)
- External beam vs brachytherapy
- Protocols range from 9 - 16 Gy in 2 to 4 different fractions
- The main side effects are dyspigmentation, dermatitis and telangiectasias
- Larger doses of therapy (usually administered as monotherapy) carry an increased risk of future skin cancer development

Laser Therapy

- 585-nm pulsed dye laser (PDL)
- 1064-nm neodymium (Nd):yttrium aluminum garnet (YAG)
- CO₂ laser
- Multiple treatments required for good outcome
- Potential for hyperpigmentation, hypopigmentation, scarring, purpura
- May be used in combination with topical applications (steroids, fluorouracil)
Systemic Treatment for Prevention of Keloids

- Prevention is better than cure

- Use anti-inflammatory and antiproliferative medications systemically to decrease the chance of recurrence and/or to prevent new lesions from appearing
Colchicine

- Disrupts cytoskeletal function by inhibiting microtubule formation
- Antifibrotic, antiproliferative, and antiinflammatory
- 4 men, 6 women (20-30 years old) all with recurrent keloids on the ear
- Colchicine started one month prior to surgery at dosage of 2 mg PO daily. Decreased to 1 mg PO daily if side-effects (diarrhea)
- Surgery with primary closure. Colchicine continued at same dose x 1 year
- No mention of use of intralesional steroids in study


Colchicine

No recurrence in any of the 10 patients after 2 years.

No lab abnormalities during the study (CBC, CMP)

The success of methotrexate in the treatment of keloids was first reported by Onwukwe (1980).

Approx 15mg twice weekly (with one week off per month) for six months post surgery, starting one to two weeks before surgery.

Methotrexate for Keloids

Prior to surgery

One year after surgery
(6 months after MTX stopped)

Methotrexate

- The success of methotrexate in the treatment of keloids was first reported by Onwukwe (1980).

- Approx 15mg twice weekly (with one week off per month) for six months post surgery, starting one to two weeks before surgery.

- For syndactyly with associated digital overgrowth, methotrexate has been used to suppress keloid formation after release of syndactyly and for control of recurrence after surgery.

- Monitoring of CBC, LFTs required.

Methotrexate after Syndactyly Release

Pentoxifylline

- Xanthine derivative and a phosphodiesterase inhibitor
- Reduces inflammation and improves blood flow
- Current uses:
  - Claudication (peripheral artery disease)
  - Raynaud’s phenomenon
  - Sickle cell disease
- Has also been shown to inhibit fibroblast proliferation and collagen synthesis in vitro

Wong et al reports 3 patients with large keloidal plaques placed on pentoxifylline

- All three patients had substantial improvement in their pain and pruritus
- Keloidal lesions did not regress but growth was halted

Pentoxifylline

- Dosage: 400mg extended-release tablets BID-TID with meals
- Does not require lab monitoring
- Contraindications:
  - recent cerebral and/or retinal hemorrhage
  - intolerant to methylxanthines (caffeine, theophylline, theobromine)
  - on anticoagulants
- Improvement in pain/pruritus within 1-2 weeks
- Used to treat patients with multiple keloids, patients with symptomatic keloids or to prevent recurrence after surgical removal
- Patients kept on pentoxifylline for at least 6 months post-operatively, +/- intralesional steroids

Summary

- Keloids are the result of an exaggerated response to wound healing
- Aims of treatment include cosmetic improvement, relief of symptoms, and prevention of occurrence or recurrence
- Multimodal treatment strategy is key to minimizing risk of keloid recurrence
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