

Keloid after orthopedic surgery: prevention, current therapy modalities, and emerging therapies modalities



Andrew Sutheno^{1*}

ABSTRACT

Keloid is a benign fibroproliferative tissue growth that exceeds the initial wound margins. It is caused by the disruption in the wound healing phase with increased fibroblast activity and excess collagen deposition. Keloid usually develops after tissue trauma. Orthopedic surgery inevitably causes tissue trauma that will lead to the formation of keloids in a few patients. Keloids can cause cosmetic and functional problems, thus interfere with a person's quality of life. Keloid therapy modalities are mainly divided into three, which are prophylactic therapy modalities, current therapy modalities, and emerging therapy modalities that are being developed. This literature review aims to evaluate further prevention, current therapy modalities, and emerging therapies modalities in Keloid following orthopedic surgery.

Keywords: Keloid, Orthopaedic Surgery, Prevention, Management.

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¹Santo Antonius Hospital, West Kalimantan, Indonesia

*Corresponding author:
Andrew Sutheno;
Santo Antonius Hospital,
West Kalimantan, Indonesia;
andrew.sutheno@gmail.com

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INTRODUCTION

Keloid is a benign fibroproliferative tissue growth that exceeds the initial wound margin in individuals with genetic susceptibility without spontaneous regression.^{1,2} The term 'keloid' comes from Greek which means crab claws due to the nature of the growth of keloid tissue that exceeds the initial wound margin.^{2,3} Keloid usually develops after tissue trauma. Orthopedic surgery inevitably causes tissue trauma that will lead to keloid formation in a few patients.⁴ Keloids can cause cosmetic and functional problems.

Keloids often cause a cosmetic problem that leads to the embarrassment of the patient and decreased self-esteem. Most importantly, keloids in joints can cause joint contractures, thus limiting joint movement. Problems that arise due to keloids can interfere with a person's quality of life.⁵

Based on the brief explanation above, this literature study aims to review the prevention and management of Keloid after orthopedic surgery.

PATHOGENESIS OF KELOID

Keloids are considered the end product of the abnormal wound healing process. In general, there are 3 phases of wound healing that consist of the inflammatory phase, the proliferation phase, and the remodeling phase. After the injury, platelet degranulation, complement activation, and a clotting cascade form fibrin clots for hemostasis. Platelet degranulation will cause the release of various cytokines, including transforming growth factor-*b* (TGF-*b*), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and insulin-like growth factor-1 (IGF-1), which play a role as a chemotactic agent to recruit neutrophils, macrophages, epithelial cells, mast cells, endothelial cells, and fibroblasts. Within 48-72 hours of injury, the wound healing process will enter a proliferation phase which can last 3-6 weeks. Fibroblasts will synthesize an extracellular matrix consisting of procollagen, elastin, proteoglycans, and hyaluronic acid, which functions to repair wound structures and form wound bridges. After the wound is closed, the wound healing phase enters a remodeling

phase which can last for several months. Excess extracellular matrix formation will be degraded by matrix metalloproteinase (MMP).⁶

Abnormal fibroblast proliferation is the main basis for keloid formation. Keloid fibroblasts proliferated more rapidly than fibroblasts from hypertrophic scars with higher collagen formation. Besides, increased inflammatory response and imbalance between deposition and degradation of the extracellular matrix also play a role in the pathogenesis of keloids. There is a balance between the inflammatory, proliferation and remodeling phases in the normal wound healing process.² In Keloid, there is a prolonged inflammatory phase, increase fibroblast activity, and excess deposition of the extracellular matrix. This causes keloid tissue to grow beyond the margins of the initial wound.⁶

CLINICAL MANIFESTATION OF KELOID

Keloid has the clinical appearance of a pink to purplish solid mass with a shiny surface, well-defined borders, and irregular edges.

Keloids can be accompanied by itch and pain. The predilection for keloids is the chest, shoulders, earlobe, and upper arm. Keloids usually form after a tissue trauma, although they can even form spontaneously in the chest area without prior trauma. Keloid tissue grows beyond the initial wound margin and there is no spontaneous regression.⁶ Keloids should be differentiated from hypertrophic scars. In hypertrophic scars, the scar tissue formed does not exceed the initial wound margin and spontaneous regression may occur. Hypertrophic scars are more common than keloids, with an incidence of 40-70% after surgery. Hypertrophic scars can be observed 4-8 weeks after injury, develop rapidly for up to 6 months, then regress gradually over several years.^{1,6}

PROBLEMS ARISING FROM KELOID

Keloids can cause cosmetic and functional problems.⁵ A study by Gürbüz et al. showed that children with elbow fractures accompanied by keloid lesions should be followed up for possible neurologic deficits with late-onset.⁷ The causative factor of late-onset neurologic deficits is the penetration of the callus to the nerve and neural fibrosis. Neural fibrosis could be precipitated by excessive fibroblastic activity.⁷ Most importantly, keloids in joints can cause joint contractures, thus limiting joint movement.⁵

Keloids often cause a cosmetic problem that leads to the embarrassment of the patient and decreased self-esteem. A study by Motoki et al. shows that 40% of keloid patients have a negative picture of their bodies.⁸ In addition, keloid patients may have body dysmorphic disorders because pathological scar tissue causes dissatisfaction with self-image. This can interfere with the patient's social relationships with other people.⁸ Keloids can cause anxiety disorders, depression, and disruption to a patient's daily routine. Problems that arise due to keloids can impair a person's quality of life.⁵

KELOID IS A PREDICTOR OF COMPLICATION IN ORTHOPAEDIC SURGERY

Keloids could also act as a predictor of complications in orthopedic surgery.

Patients diagnosed with keloids are at an increased risk of arthrofibrosis after primary total knee arthroplasty (TKA). Arthrofibrosis is reported to be the leading cause of TKA failure. Both keloids and arthrofibrosis are associated with an overexpression of TGF- β 1. Patients who reported stiffness from arthrofibrosis usually require surgical intervention such as manipulation under anesthesia, which consists of manipulating the knee through a full range of motion while sedated. They are also at a higher risk of lysis of adhesion, an open or arthroscopic approach to access and debride adhesion.⁹

TREATMENT OF KELOID

According to some recent literature, keloid therapy modalities are mainly divided into prophylaxis therapy, current therapy, and emerging therapy modalities that are being developed.^{5,10-12}

A. PROPHYLAXIS THERAPY

Skin Incision along the Main Folding Lines

The formation of hypertrophic scar and keloids could be prevented by making the skin incisions along the main folding lines.^{13,14} The skin tension lines depend on the interrelation of elastic fibers and collagen fibers and the anchorage of collagen bundles on each other. Incisions parallel to folds separate the collagen bundles longitudinally and heal without retraction. A linear incision develops a wider gape if it occurs transversely to the main folding lines.¹³

Compression Therapy

Wound compression with a pressure of 15-40 mmHg for more than 23 hours a day for at least 6 months has been said to prevent keloids. Although this pressure therapy reduces scar tissue's subjective and objective complaints, the scientific evidence supporting its clinical effectiveness is controversial. The mechanism of pressure therapy to prevent keloids has not been elucidated, but it is hypothesized that pressure therapy can cause occlusion of blood vessels, thereby limiting oxygen intake from blood vessels to the injured tissue, which leads to increased apoptosis.¹⁰

Silicon

Silicone sheets can prevent wound stretching, provide occlusion, and hydrate the surface of the wound tissue. The silicone sheet should be used as early as 2 weeks from the start of the wound for more than 12 hours a day. This silicone sheet can be used for a minimum of 2 months.¹⁰

Flavonoid

Flavonoids or bioflavonoids are natural substances from various plants that have been used to prevent the formation of heavy scar tissue. Several studies have shown good results from using flavonoid gel on scars, but the efficacy of this product is controversial. The mechanism underlying the use of flavonoids in scars is through the induction of matrix metalloproteinase-1 (MMP-1) and inhibition of small mothers against decapentaplegic 2 (SMAD 2), SMAD 3, SMAD 4 protein expression. The recommendation use of flavonoid is 2 times a day for 4 to 6 months.¹⁰

B. CURRENT THERAPY MODALITIES

Triamcinolone acetonide (TA)

Intralesional TA injection is the most frequently used therapeutic modality for keloid management, but it is estimated that 50% of keloids are resistant to steroid therapy.¹⁵ Triamcinolone acetonide works by suppressing the inflammatory process, decreasing fibroblast proliferation, and decreasing collagen synthesis. Side effects of TA that often occur include telangiectasis, hypopigmentation, and skin atrophy. These side effects were reported to be reduced when combined with 5-fluorouracil for keloid management.¹⁶

5-Fluorouracil (5-FU)

5-fluorouracil is a pyrimidine analog that inhibits DNA synthesis by irreversibly inhibiting the thymidine synthase enzyme, which triggers fibroblast apoptosis and scar degradation.¹⁷ The 5-FU concentration commonly used as a keloid monotherapy agent is 50 mg/ml. Fitzpatrick recommends a one-week interval between intralesional 5-FU injections for the management of keloids. The use of intralesional 5-FU injection as a monotherapy agent in the management of keloids has been reported to be good for

45-78% of patients.¹⁸

Surgery scar revision

Scar revision with surgical excision of the Keloid should be performed with minimal tension at the time of wound closure. The recurrence rate of keloids after scar revision with surgical excision is reported to be high, namely 45-100%. This surgical excision scar revision often must be combined with other therapeutic modalities, such as steroid injection and radiotherapy to prevent keloid recurrence.¹⁰

Cryotherapy

Cryotherapy has been used to manage keloids, both as a single therapeutic agent or in combination with other therapies such as intralesional TA injection. Cryotherapy could induce tissue necrosis due to vascular damage, thus can be used as a keloid therapy. Cryotherapy success rates are reported to be 32-74% after several therapy sessions.¹⁰

Radiotherapy

Radiotherapy is generally performed as adjuvant therapy and is performed 24-48 hours after surgical scar revision. The radiation dose used is 40 Gray which is divided into several therapy sessions to minimize side effects. Radiotherapy is thought to have an anti-angiogenic effect so that it can be used in the management of keloids. Inhibition of angiogenesis will reduce inflammatory cytokines and inhibit fibroblast activity, thereby reducing collagen synthesis and suppressing keloid formation. The unwanted side effect that arises from radiotherapy is the risk of carcinogenesis. In one study, keloid recurrence with radiotherapy was reported to be 9.59%.^{10,19}

Laser

The first laser therapy was used for keloid therapy in 1980. The most commonly used laser for keloid therapy is the pulsed dye laser with a wavelength of 585 nm. Another laser frequently used for keloid management is the 1064 nm neodymium-doped yttrium aluminum garnet (Nd: YAG) laser. Several sessions of laser therapy are required for keloid management. The laser will cause damage

to blood vessels, thereby inhibiting the delivery of inflammatory cytokines to the keloid tissue. Side effects that can arise from a laser are hyperpigmentation, hypopigmentation, bullae formation, and purpura.²⁰

C. EMERGING THERAPY MODALITIES

Interferon

Interferon consists of cytokines that have anti-proliferative and anti-fibrotic effects. Interferon will decrease collagen synthesis and fibroblast proliferation by decreasing TGF- β 1 expression. Interferon intralesional injection is usually used at a dose of 1.5 million IU, 2 times a day for 4 days. The side effects reported are pain at the injection site and flu-like symptoms. Although interferon is an expensive therapy for keloids, it has become a promising therapeutic modality.²¹

Bleomycin

Bleomycin is a cytotoxic, anti-neoplastic, anti-viral, and anti-bacterial agent derived from *Streptomyces verticillus*. Bleomycin could reduce collagen synthesis and induced apoptosis. Bleomycin 1.5 IU / ml was given by intralesional injection 1 month apart. Generally, it takes 2-6 sessions. Several studies have shown complete keloid depletion in 54-73% of keloid patients and relief of keloid symptoms such as itching and pain. Side effects that can be found are pain on injection, ulceration, hyperpigmentation, and skin atrophy. Systemic side effects have not been reported.¹⁰

Verapamil

Verapamil is a calcium channel blocker that is used as an anti-hypertensive agent. Verapamil works by decreasing collagen production, stimulating collagenase synthesis, and reducing fibrotic tissue production. There were no systemic side effects associated with intralesional verapamil injection.²¹

Imiquimod

Imiquimod, 5% cream, can be used as a therapeutic agent for keloids because it promotes apoptosis. The use of 5% imiquimod cream after excision of the Keloid on the ear lobe for 6 weeks

shows good cosmetic results. Side effects reported include erythema, erosion, and crust formation. A meta-analysis in 2017 estimated the recurrence of keloids in patients receiving imiquimod cream after surgery was 24.7%.¹¹

Tamoxifen

Tamoxifen is an anti-estrogen agent used in the management of breast cancer. In the in vitro studies, tamoxifen decreased TGF- β 1 production, inhibited the proliferation of keloid fibroblasts, and decreased collagen synthesis. A clinical study in 13 keloid patients injected with tamoxifen 20 mmol/L once a week for 8 weeks showed a reduction in the number of keloid fibroblasts on the histopathological examination compared to before therapy.¹¹ Besides, the collagen structure is also found to be atrophic.¹¹

Type-A Botulinum toxin

Botulinum toxin derived from *Clostridium botulinum* is a neurotoxin that inhibits neuromuscular transmission. Several studies have shown that botulinum toxin type A can minimize scar formation by reducing muscle tension during wound healing. In addition, botulinum toxin can cause the cell cycle to stop at G0 or G1 and affect TGF- β 1 expression. Intralesional botulinum toxin injection at a dose of 70-140 U per session at intervals of 1-3 months for 3 sessions showed improvement in keloid lesions and decreased Keloid subjective symptoms itching and pain.^{10,22}

Captopril

Research by Chen et al. shows that captopril can reduce the production of angiotensin II, collagen, and cellular proliferation in keloid fibroblast cultures at certain effective concentrations.²³ Captopril also dramatically decreased the expression of TGF- β 1, PDGF, and heat shock protein 47 (HSP47) in keloid fibroblasts. Through these various mechanisms, captopril has been shown to inhibit fibroblast proliferation and collagen synthesis, which plays a role in keloid formation. This makes captopril a potential drug to be used as a modality for keloid therapy.²³

Mesenchymal stem cell

Mesenchymal stem cells have immunomodulatory and anti-fibrotic

effects. The anti-fibrotic effect of mesenchymal stem cells in various fibrotic diseases such as myocardial infarction, renal fibrosis, or cirrhosis of the liver has been reported. Mesenchymal stem cells can reduce the excess inflammatory process that occurs in keloids. This therapy can be given by systemic injection or local injection to the wound, intradermal, or subcutaneous. Several mechanisms are thought to underlie the use of mesenchymal stem cells in keloid management, which inhibit pro-inflammatory cells, anti-fibrotic activity through decreased production of collagen types I and III, and stimulating angiogenic activity that helps normal wound healing. Although most studies report anti-fibrotic effects, some studies report proinflammatory effects of mesenchymal stem cells, so that further investigation is needed before being used as a modality of keloid therapy.¹⁰

CONCLUSION

Orthopedic surgery inevitably causes tissue trauma that will lead to the formation of keloids in a few patients. Keloids can cause cosmetic and functional problems, thus interfere with a person's quality of life. There are various prophylaxis modalities to prevent the formation of Keloid in orthopedic surgeries. If the Keloid has been developed, current therapy modalities, such as intralesional TA injection, 5-FU, laser, radiotherapy, cryotherapy, and surgical scar revision, can be used. Many emerging therapy modalities are being developed to maximize the keloid treatment strategies.

CONFLICT OF INTEREST

There is no competing interest regarding the manuscript.

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AUTHOR CONTRIBUTION

Andrew Sutheno is responsible for this literature study from the conceptual framework, data acquisition, selecting

the literature, as well as data analysis and interprets the study through publication.

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