Case Report

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Fractional Laser As Laser Assisted Drug Delivery of Triamcinolone Acetonide in Keloid

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Abstract

Background: *Keloid is benign hyperplasia of dermal collagen which may or may not be preceded by injury in susceptible person. Keloids are refractory to treatment most of the times. Intralesional corticosteroid, topical retinoic acid, topical imiquimod cream, surgery, cryotherapy, laser, and silicon sheeting are mainly used for treatment. Fractional ablative laser is a new laser treatment modality that create numerous microscopic thermal injury zone controlled width, depth, and density that are surrounded by a reservoir of spared epidermal and dermal tissue, allowing of rapid repair of laser-induced thermal injury. Multiple studies demonstrate that laser pretreatment of the skin can increase the permeability and depth of penetration of topical drug molecules.*

Main observations: *A boy, 12 years, scar that arise after burn scar 14 months ago. Scar was felt bigger and thickening also itching. Patient was diagnosed keloid and had been treated with same-session ablative fractional laser and topical triamcinolone acetonide after therapy. Patient had been treated 5 sessions with 3 weeks of interval. Successful of treatment was measured with reduction of keloid size and vancouver scar scale (VSS).*

Conclusions: *Laser assisted drug delivery is an envolving technology with potentially broad clinical application. Ablative fractional laser treatment create vertical channels that might assist the delivery of drug into skin. Combination same-session therapy with ablative fractional laser and triamcinolone acetonide offer a good combination caused assisted delivery of drug.*

Keywords: Fractional Laser, Keloid, Laser-Assisted Drug Delivery, Microthermal Zone, Triamcinolone Acetonide

Introduction

Keloid is a hyperproliferative reaction of the connective tissues due to trauma which often occurs at skin undergoing strong strecthing [1]. Keloid is commonly found in Africans, Latin Americans and Asians with an incidence of 4,5-16%. Women have a higher predisposition in certain ethnicities [2,3]. The incidence of new keloid cases at the Dermatology and Venereology (DV) clinic at the Dermatocosmetology (DC) Division of Dr. Muhammad Hoesin Palembang Hospital (RSMH) in 2016 are 4 women and 3 men.

The ethiological factors of keloid are trauma, skin stretching, wound infection, endocrine factors such as estrogen and *melanocyte stimulating hormone*, and genetic factors. The exact pathogenesis of keloid is still not clear to this day, but it is assumed that an increase of collagen synthesis not accompanied by collagen degradation increase plays a role in it. In normal wound healing, several signals are sent to fibroblasts surrounding the wound, which induces the cells to fill the wound by increasing collagen and *glycosaminoglycan* production [1,3].

Keloid is difficult to eliminate and has a high tendency of relapse. Topical and intralesion steroids are currently the best choices for therapy, but its efficacy are limited. The main effect of corticosteroids is to suppress wound inflammation, decrease collagen and *glycosaminogly*can synthesis, inhibit fibrosis, and increase collagen and fibroblast degradation [4]. Intralesion corticosteroid commonly used is triamcinolone acetonide [5]. Recent studies reported that fractional ablative laser may mediate topical drug delivery [6,7].

Laser stands for *Light Amplification by the Stimulated Emission of Radiation*, and is a high intensity light [8]. Laser produces a high intensity light which has a one-way direction [9]. Fractional ablative laser will create an ablative zone with variating depths,

which will induce wound healing and collagen production response. Theoretically, fractional ablative laser will facilitate the penetration and distribution of topical drugs, due to channel of laser that has the ability to reach the dermis thus facilitating drug delivery [6,7].

In this case report, keloid is treated with fractional ablative laser followed by topical acetone triamsolone application. This case report is to increase knowledge regarding keloid pathogeneisis, fractional ablative laser mechanism and drug delivery.

Case Report

A boy, 12 years, scar that arise after burn scar 14 months ago. Scar was felt bigger and thickening also itching. Physical examination status: regio *antebrachii sinistra 1/3distal*: scar hyperpigmentation, soliter, ireguler, 2,2x1,0,5 cm, smooth surface, consistency rough, no tenderness upon palpation. Vancouver scar scale (VSS) this patient was 6 at admission. Patient was diagnosed keloid. Patient had been treated with ablative fractional laser and topical triamcinolone acetonide after therapy. Each of treatment had 3 weeks of interval. Successful of treatment was measured with reduction of keloid size and VSS. At session 5 size of keloid was reduce into 1,8x1x0,3 cm and VSS was 5.

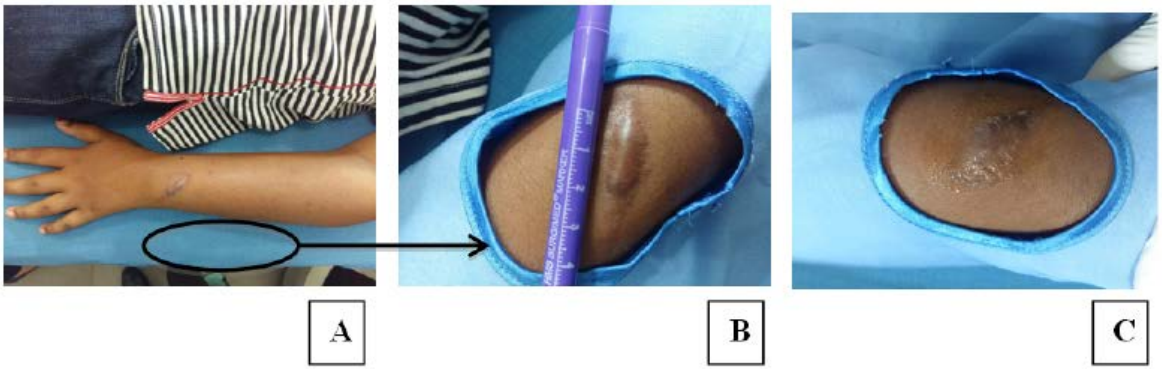

Figure1: Keloid picture at admission (a,b) Regio *antebrachii sinistra 1/3 distal* (c) post fractional laser with triamcinolone acetonide application

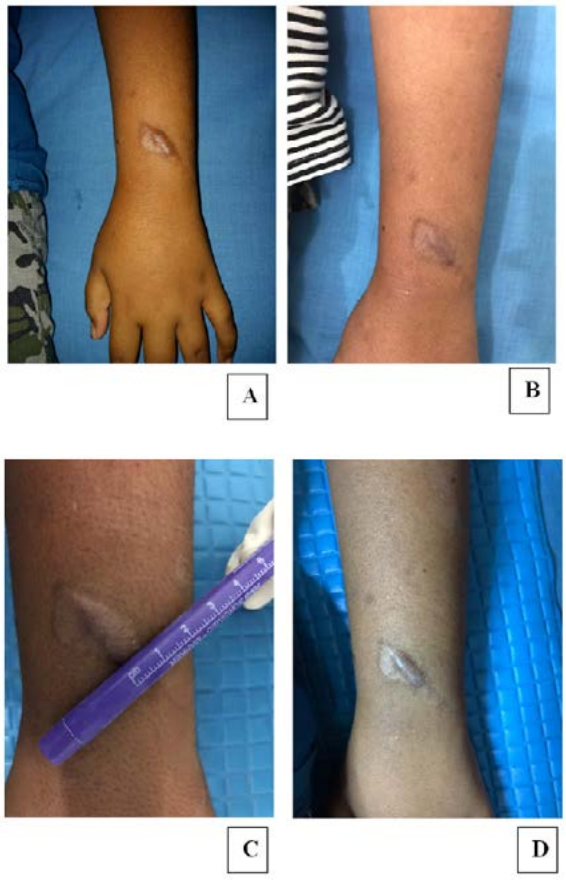

Figure 2: a) Keloid picture at follow up session 2, b) Keloid picture at follow up session 3, c) Keloid picture at follow up session 4, d) Keloid picture at follow up session 5.

Discussion

Keloid is an aggravated fibrosis response with well-defined borders and growth surpassing the initial lesion borders. Keloid is usually accompanied by pain and pruritus. Skin trauma on the reticular dermis or deeper layers may cause hypertrophic scars and keloids. Several factors reported as the ethiology of keloid are acne, folliculitis, varicella, vaccination, ear piercing, laceration wounds and surgery wounds. Keloid is reporte occur both in dominant and recessive autosomal conditions, and is correlated with *Human Leukocyte Antigen* (HLA) factors B14, B21, BW16, BW35, DR5, and DQW3. Keloid may occur in one month to one year after trauma of inflammation [10,11]. The incidence of keloid is similar in men and women in the age range of 10-30 years old. Keloid incidence increases by 16% in individuals with dark pigmented skin such as Africans.

The pathogenesis of keloid is still not clear, but it is known that an 20-fold increased synthesis of collagen occurs in keloid. Excess collagen deposition in keloid is caused by collagen synthesis incrase, collagen degradation decrease or combination of both. In normal wound healing, after complete repair TGF- β will decrase, leading to regression of connective tissue elements. Keloid occurs as a result of prolonged inflammation and increase of several growth factors such as *platelet derived growth factor* (PDGF), *transforming growth factor-β* (TGF-β1), TGF-β2 and *vascular endothelial growth factor* (VEGF). This is followed by a decrease in apoptosis, increase in bcl-2 and a mutation on the p53 gene. An increase in collagenase not accompanied by an increase in collagen degradation lead to increased α-globulin deposition and collagenase inhibitors in the keloid serum [1,12]. *Transforming growth factor*-β plays a role in fibroblas proliferation and collagen production. In keloid tissues, there is an excess production and dysregulation of TGF-β. Increased TGF-β will induce *tissue inhibitor of metalloproteinase* (TIMP-1) synthesis which inhibits collagen degradation. There is also a decrase in the production of factors that control *metalloproteinase* (MMP) [3].

The diagnosis of keloid is confirmed based on patient history and phsyical examination. The patient in this case reported a brownish mass on a previous burn wound at his left arm which gradually increases in size and accompanied with pruritus. Physical examination status: regio *antebrachii sinistra 1/3 distal*: scar hyperpigmentation, soliter, ireguler, 2,2x1,0,5 cm, smooth surface, consistency rough, no tenderness upon palpation.

Several available therapy modality are: (1). Pharmacology, both topical (corticosteroid, retinoid, and imiquimod) and injection (corticosteroid, interferon, 5-Fluorouracil (5-FU), and bleomycin); (2). Surgical debulking or laser debulking; and (3) physical therapy such as laser, radiation, compression, silicon sheeting, and cryotherapy. The first line therapy of keloid is intralesion corticosteroid, and the second line therapy are intralesion 5-FU injection, intralesion bleomycin, surgery, radiation and laser [10]. In the clinical guidelines of Dermatology and Venereology of PERDOSKI 2014, treatment of keloid are corticosteroid injection and intralesion 5-FU injection, cryosurgery, surgical intervention and radiation.

Intralesion corticosteroid injection is the main treatment of keloid. The dose of triamcinolone acetonide is based on lesion's size, location and patient's age. The dose range is 10-40 mg/mL with interval of 3-4 weeks between administrations [5]. Intralesion administration is aimed to create a high concentration in the lesion location with minimal systemic absorbance. Corticosteroids are actively transported towards target cells and immediately binds with intracellular steroid cytoplasmic receptors *glucocorticoid response elements* (GRE). GRE binding will affect specific gene transcriptions which will either inhibit or accelerate the production of specific mRNAs [13]. The mechanism of triamcinolone acetonide is by reducing inflammation, in which this drug inhibits the migration of inflammation cells and phagocytosis. The vasoconstriction effect of the steroid will disturb oxygen and nutrition routes towards the wound and its antimitotic properties affect fibroblasts and keratinosit. Corticosteroid increases collagen degradation by inhibiting macroglobulin-α2 which acts as a collagenase inhibitor, thus inducing collagen degradation. Corticosteroid affects the extracellular matrix produced by fibroblasts by manipulating the transcription of growth factors. The main *growth factor* in wound healing is *tumour growth factor* (TGF-β1), which synthesize extracelullar matrix and inhibit extracelullar matrix degradation which in turn induce fibrosis [1,3].

The success rate of intralesion corticosteroid injection in keloid is 50-100%. Corticosteroid injection is an effective monotherapy in reducing lesion volume in a majority of patients. Previous literatures showed that a decrase of mean lesion volume from 0,73±0,701 mL on the baseline to 0,14 ± 0,302 mL after intralesion triamcinolone acetonide is observed. The side effects of this procedure are pain on the injection area, atrophy and thinning of the skin and subcutaneous tissues, linear hypopigmentation and a high recurrence rate ranging from 9-50%. Serious side effects include local skin necrosis, ulcers and Cushing syndrome. Growth resriction is a characteristic of Cushing's syndrome in children. This is due to the decrease of *growth hormone releasing hormone* (GHRH) and the direct effect towards the *growth plate* with inhibition of IGF-1 [13]. Complications may be managed by dosage adjustment and combination with other agents [5]. The dose of triamcinolone acetonide is 10 mg/mL, and in this case a total of 0,1 cc/cm^2 was given (2 mg), equivalent with prednisone 2,5 mg. The physiological dose of prednisone is 7,5-10 mg, and because this patient received a dose below the physiological dose no apparent systemic corticosteroid side effects, such as Cushing's syndrome, were observed. In this case report the patient is a child, and triamcinolone acetonide injection may cause inadherence due to pain. Laser usage can distribute drug delivery more equal and deeper. There are several case reports regarding the success of keloid management using fractional laser followed by acetone triamsolone with satisfying results.

Skin is the most outer surface of the human body which protects its from surrounding environment, and also supports interaction with the environment. The skin comprises of 3 layers; epidermis, dermis, and hypodermis. The stratum corneum is the outer layer of the epidermis, which comprises of corneosit components rich of protein and intercellular lipid between corneosit known as *brick* and *mortar*. The dermis comprises of collagen, elastin tissue, blood and lymphatic vessles, and skin appendages [14].

Stratum corneum is not permeable with large molecules (molecule mass more than 500 Dalton) and is not water absorbant. After passing stratum corneum, molecule transportation to a deeper cutaneous level becomes easier. The movement of molecules is the primary factor in drug delivery [15]. A topical drug delivery occurs kinetically and according Ficks's Laws of diffusion, in which the absorbance of

substance (J) is results of particle's coefficient (Km, which reflects the amount of available molecules to spread across the membrane), constant distribution (Dm, which reflects the molecule's ability to pass the membrane) and concentration difference of molecules on both barriers' sides (ΔC) divided by route length (L) [15,16]. There are several strategies to increase topical drug delivery such as electroforation (*electropermeabilitation*), sonophoresis (*thermal and cavitation*), and *microneedles* [16].

$$J = \frac{KmxDmx\Delta C}{L}$$

Laser therapy is a unique modality that has ability to create a predictable and controlled destruction of the epidermis and dermis layers of the skin. Fractional laser is based on the method of energy distribiution of the laser on the skin, where a portion "*fraction*" is heated in microscopic columns called *microthermal zones* (MTZs). Fractional laser is divided in two types; ablative and non-ablative lasers.[9,17] The types of fractional ablative lasers available are CO2 (10,600 nm) lasers and erbium lasers (Er: YAG, 2940nm) [7]. Components that may absorb this wavelength is water. In ablative fractional laser there is an evaporation of tissues on MTZs, causing open wounds [9,17].

Fractional ablative lasers create a vertical channel on the skin known as MTZ [9]. This channel create direct way for drug penetration. In vivo, fractional ablative laser facilitate substance delivery across the inner dermis [7]. MTZs are characterized by its 100 µm length and distributed in a *grid-like* pattern which appears as small dots or pixels on the skin surface. Fractional laser MTZ penetration depends on the energy, and is able to be controlled on the desired area with a depth range of 300 µm-1,5 mm. Tissues not included in the MTZs acts as the regerartion reservoir cells which may migrate to the treatment area and accelerate healing. Histologic evaluation shows homogenic dermal matrix and microscopic debris necrosis, indicated by destruction of the outer component of the epidermis caused by keratinosits on the lateral margin of the MTZ.[9,17] Laser-assisted drug delivery is an alternative delivery route besides injection or other topical delivery routes. Fractional ablative laser is a promising method with minimal pain and fast recovery [4,6].

The increase of molecule penentration across MTZs are best understood with *Fick's law*. In fractional ablative lasers, an increase of the stratum corneum (Km) permeability through MTZs occurs, thus increaseing the overall drug absorption rate, molecule size determines the absrption rate, thus a laarger molecule will cause a higher resistance in their movement and decrease Dm, reducing the absorption rate [15]. Fractional ablative laser may increase corticosteroid delivery by creating MTZs with a more distributed penetration, in which the drug will reach the dermis level equally [6].

Several previous studies supported this case report, such as Cavalie et al who reported improvement in 23 keloid cases managed with 2940 nm fractional ablative laser (erbium) with an energy of 180 J/m2 followed by topical bethametason cream twice a day, in which a recovery rate of 50% was achieved [4]. Waibel et al on their study on 15 hypertrophic scar patients managed with fractional ablative laser followed by topical triamcinolone acetonide 10 mg/dl immediately with an interval of 2-3 month found a improvement score of 2,73 (scale 0-3) on 11 patients [6]. In this case, we use Unixel 30, wavelength of 10.600 nm, energy 3 W, 1 *point of shot* followed by 10 mg/mL topical triamcinolone acetonide with an interval of 3 weeks, in which decrased in Vancouver score was observed.

Keloid have a high recurrency despite the choice of treatment [1,5]. The *quo ad vitam* prognosis of this patient is *bonam* due to the lack of life-threatening situations, the quo ad *fungsionam* prognosis is *bonam* due to no disabilities in daily activities, and the *quo ad sanationam* prognosis is *dubia ad bonam* due to the lack of a perfect management of keloid and its high recurrence rate [18].

Conclusion

We reported a case of keloid in a child who previously had a burn wound in his left arm 14 months ago. The lesion improved in reduction of keloid size and VSS after therapy with fractional ablative laser followed by triamcinolone acetonide application. Fractional ablative laser mediates the delivery of drugs through the *microthermal* zone. In this particular case, fractional ablative laser followed by triamcinolone acetonide application is well tolerated with no apparent side effects. Further studies are needed to determine the drug delivery efficacy in fractional ablative laser therapy.

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