A COMPARATIVE STUDY ON THE EFFICACY OF COMBINATION WITH PULSED DYE LASER AND INTRALESIONAL CORTICOSTEROID INJECTIONS VERSUS INJECTIONS ALONE FOR TREATMENT OF KELOID AND HYPERTROPHIC SCARS

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IN
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Thesis Title	A Comparative Study on The Efficacy of Combination with Pulsed Dye Laser and Intralesional Corticosteroid Injections Versus Injections Alone for Treatment of Keloid and Hypertrophic Scars
Author	Parima Prachayarporn
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ABSTRACT

The objective of the study was to compare the efficacy of combination of pulsed dye laser and intralesional corticosteroid injections versus injections alone for treatment of keloid and hypertrophic scars. Eighteen Thai subjects with keloid and hypertrophic scars received three split-scar monthly treatments, one side with intralesional corticosteroid injections, and the other with pulsed dye laser and intralesional corticosteroid injections. The improvement of scars and side effects were evaluated at every treatment sessions and four weeks after the last treatment. The study found significant improvement in keloid and hypertrophic scars after treatment in both group without statistically significant difference between them. The side effects of both group were hyperpigmentation and telangiectasia. In conclusion, Intralesional corticosteroid injections alone and its combination with pulsed dye laser are effective modalities that could be used for treatment keloid and hypertrophic scars. The adjunctive use of pulsed dye laser did not significantly enhance clinical outcome in our study except in terms of increased scar's elasticity.

Keywords: Keloid/Hypertrophic scars/Pulsed dye laser/Intralesional corticosteroid injection

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CHAPTER 1

INTRODUCTION

1.1 Background

Hypertrophic scars and keloids are common in Thai patient that mainly dermatologists and plastic surgeons encounter. Excessive scars form as a result of aberrations of physiologic wound healing and may develop following any insult to the deep dermis or following damage to more than 33.1% of the thickness of the skin (Baker, Urso-Baiarda, Linge & Grobbelaar, 2009) through burn injury, lacerations, abrasions, surgery, piercings and vaccinations. By causing pruritus, pain and contractures, excessive scarring can dramatically affect a patient's quality of life, both physically and psychologically (Gauglitz, Korting, Pavicic, Ruzicka & Jeschke, 2011).

Excessive scarring was first described in the Smith papyrus about 1700 BC. Many years later Mancini (in 1962) and Peacock (in 1970) differentiated excessive scarring into hypertrophic and keloid scar formation. Per their definition, both scar types rise above skin level, but while hypertrophic scars do not extend beyond the initial site of injury, keloids typically project beyond the original wound margins. (Gauglitz et al., 2011)

Abnormal or raised dermal scars in the form of keloid and hypertrophic scar occure during an abnormal wound healing process that can be temporally grouped into four distinct phases hemostasis, inflammation, proliferation and remodeling. Abnormal collagen synthesis and proliferation of fibroblasts lead to excessive production of fibrous tissue then keloid and hypertrophic scar formation.

Keloid formation is seen in individuals of all races, except albinos, but dark-skinned individuals have been found to be more susceptible to keloid formation, with an incidence of 6% to 16% in African populations. The concept of a genetic predisposition

to keloids has long been suggested, because patients with keloids often report a positive family history (Gauglitz et al., 2011).

There is no universally accepted treatment resulting in the permanent removal of keloid. Due to its high recurrence rates and unknown resolution rates, keloids present a challenge to both the patient and clinician. Many therapies have been advocated with varying levels of success. Different treatment modalities such as radiation, pressure therapy, cryotherapy, interferon 5-fluorouracil (5-FU), topical silicone, surgery and intralesional steroid injections have been used for the treatment of keloid and hypertrophic scar with varying degrees of success (Ud-Din, Bowring, Derbyshire, Morris & Bayat, 2013).

Intralesional corticosteroid injections when used alone, can soften and flatten keloid and hypertrophic scar provide symptomatic relief but they cannot make these scars disappear. Corticosteroids reduce excessive scarring by decreasing collagen synthesis, which could be due to first, the interruption of the inflammatory cell migration and phagocytosis. Second, it induces vasoconstriction resulting into deprivation of oxygen and nutrients in the wound. Third, it has an anti-mitotic activity on fibroblasts and keratinocytes (Elwakil, 2009). The efficacy of corticosteroid injections has been well established in the treatment of keloid disease. The standard and most commonly used corticosteroid is triamcinolone acetonide (TA). There is a broad consensus that TA is efficacious and is first-line therapy for the treatment of keloid scars and second-line for the treatment of hypertrophic scars. But the outcome of this treatment has been uncertain with recurrence rates between 9 and 50 % and associated with various adverse effects such as atrophy, telangiectasia and pigmentary changes (Ud-Din et al., 2013).

The pulsed dye laser (PDL) treatment of scars was first described by Alster et al in 1993, after which it rapidly became a mainstream form of laser treatment of scars. Pulsed dye laser has a high absorption coefficient for hemoglobin (Akaish, Piaaurro and Meeker, 2012). The PDL improves keloids or hypertrophic scars by inducing capillary destruction, which generates hypoxemia and in turn alters local collagen production (Gauglitz, 2013). Although PDL is more effective than argon and carbon dioxide lasers, which target the water in the skin, but a single PDL irradiation procedure have a variable results (Akaish et al., 2012). In some case-control studies did not differ from the untreated control groups after longer follow-up observation periods (Gauglitz, 2013).

Theoretically, the combination therapy of intralesional corticosteroid injections and pulsed dye laser is supposed to be of value in order to achieve better results and to minimize the associated complications. Recently, there're reported the effectiveness of this combination (Connell & Harland, 2000; Elwakil, 2009). But there's no study compare the clinical improvement and side effect of the combination of 595-nm pulsed dye laser and intralesional corticosteroid injections versus intralesional corticosteroid injections alone. We hypothesize that this combination may have a synergistic effect on keloid and hypertrophic scars and obtain the better clinical outcomes. Therefore, the purpose of this study is to compare the clinical improvement, side effect and satisfaction of the combination of pulsed dye laser and intralesional corticosteroid injections versus intralesional corticosteroid injections alone for the treatment of keloid and hypertrophic scars.

1.2 Research Question

1.2.1 Primary Question

Is the combination of pulsed dye laser and intralesional corticosteroid injections has more efficacy for treatment of keloid and hypertrophic scars than intralesional corticosteroid injections alone?

1.2.2 Secondary Question

Is the combination of pulsed dye laser and intralesional corticosteroid injections has more satisfaction and less side effect for treatment of keloid and hypertrophic scars than intralesional corticosteroid injections alone?

1.3 Objectives

To compare the efficacy of the combination of pulsed dye laser and intralesional corticosteroid injections versus intralesional corticosteroid injections alone for treatment of keloid and hypertrophic scars.

1.4 Outcome

1.4.1 Primary outcome

Compare the clinical improvement (Height, length, width) of the combination of pulsed dye laser and intralesional corticosteroid injections versus intralesional corticosteroid injections alone for treatment of keloid and hypertrophic scars.

1.4.2 Secondary outcome

1.4.2.1 Compare improvements of Height, length, width, erythema, and pliability of week 0 to each follow-up.

1.4.2.2 Compare the clinical improvement of erythema, and pliability of the combination of pulsed dye laser and intralesional corticosteroid injections versus intralesional corticosteroid injections alone for treatment of keloid and hypertrophic scars.

1.4.2.3 Compare the side effect of the combination of pulsed dye laser and intralesional corticosteroid injections versus intralesional corticosteroid injections alone for treatment of keloid and hypertrophic scars.

1.4.2.4 Compare the clinical improvement between two groups that evaluated by three independent dermatologists by compared the patients' photographs.

1.4.2.5 Compare the clinical improvement between two groups that evaluated by patient.

1.5 Research Hypothesis

The combination of pulsed dye laser and intralesional corticosteroid injections has higher efficacy and lower side effect than intralesional corticosteroid injections alone for treatment of keloid and hypertrophic scars.

1.6 The Scope of Research

Sixteen patients with keloid or hypertrophic scars, both males and females, ages 15-55, were randomly assigned to the treatment with the combination of pulsed dye laser and intralesional corticosteroid injections and intralesional corticosteroid injections alone on each half of the scar. The treatments were performed once a month for three months at Mae Fah Luang University Hospital, Bangkok Photographic records at the beginning and the 4th, 8th, and 12th weeks. At each assessment, the observer compared the photographs and measured the length, width, height, erythema, and pliability and evaluate the side effect of the lesions. Clinical improvement was independently evaluated by third party dermatologists and the patients.

1.7 Conceptual Framework

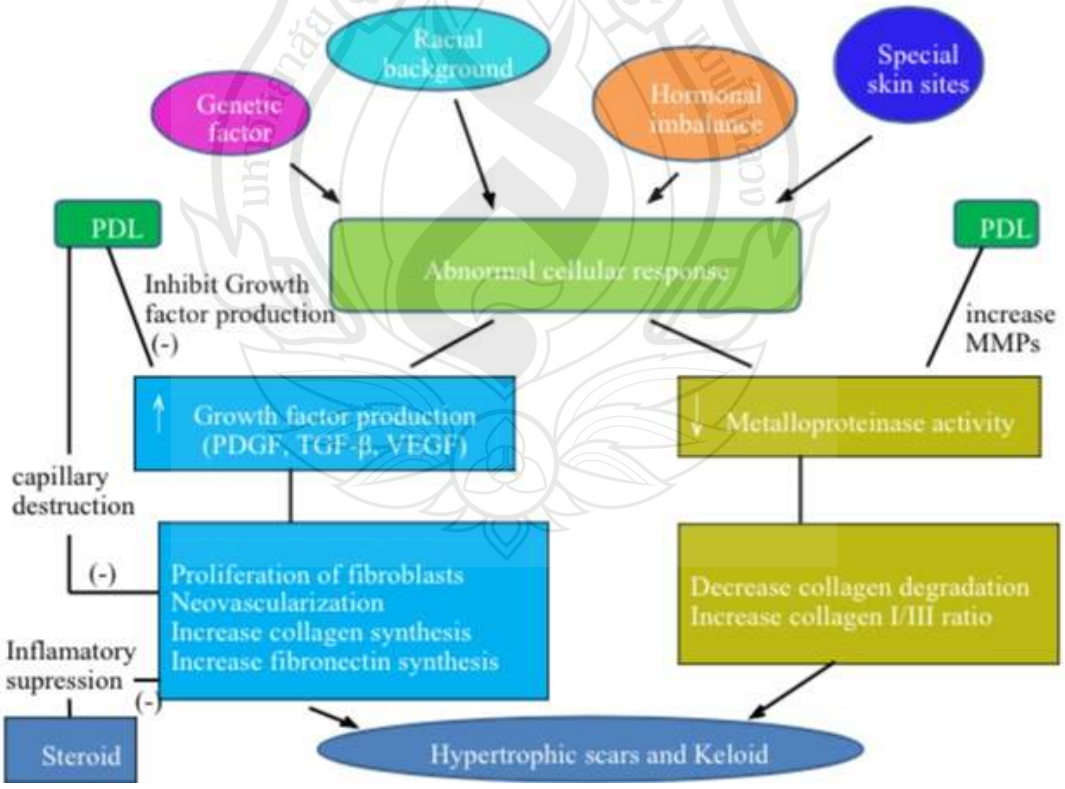


Figure 1.1 Conceptual Framework

1.8 Limitation of the Research

Limitation in terms of the duration of the study.

1.9 Operation Definitions

1.9.1 Hypertrophic scars are erythematous, raised, firm nodular growths that occur more commonly in areas subject to increased pressure or movement or in body sites that exhibit slow wound healing.

1.9.2 Keloids present as deep reddishpurple papules and nodules firm, mildly tender, with a shiny surface and sometimes telangiectasia. Projects beyond the original wound margins, often on the earlobes, anterior chest, shoulders, and upper back.

1.9.3 The pulse dye laser is a laser that has high absorption coefficient for hemoglobin. It's considered to be the criterion standard for vascular lesions, such as port wine stains, initial hemangiomas, and facial telangiectasias. Additionally, this laser type is often successfully used for non-vascular indications, such as keloids or hypertrophic scars. Currently, the PDL wavelengths 585 and 595nm are most frequently used for therapeutic purposes.

1.9.4 Triamcinolone acetonide is a synthetic glucocorticoid corticosteroid with marked anti-inflammatory action, this medication is used in a variety of conditions such as dermatitis, aloplecia areata, allergic disorders, arthritis, blood diseases etc. In the form of a sterile aqueous suspension it's suitable for intralesional and intra-articular injection.

CHAPTER 2

LITERATURE REVIEW

2.1 Normal Wound-Healing Process

Understanding the normal sequence of wound healing is important in understanding the pathophysiology and treatment of hypertrophic scars and keloids. Normal wound healing occurs in four phases: (1) Haemostasis (2) The inflammatory phase, (3) The proliferative or granulation phase, and (4) The maturation or remodeling phase.

2.1.1 Haemostasis (immediate)

Tissue injury is characterized by microvascular injury and extravasation of blood into the wound. Loss of structural integrity initiates the coagulation cascade and constriction of vessel walls the resulting clot formation and platelet aggregation limits further blood loss. The platelets trapped in the clot are essential for haemostasis and a normal inflammatory response. The platelets degranulate and release their alpha granules, which secrete several growth factors, including platelet-derived growth factor, insulin-like growth factor, epidermal growth factor, transforming growth factor-β, platelet factor-IV. These proteins initiate the wound healing cascade by attracting and activating fibroblasts, endothelial cells and macrophages. These events also activate four major amplification systems (complement cascade, clotting mechanism, kinin cascade, plasmin generation), which contribute to haemostasis and the subsequent stages of the healing process.

However, healing can occur in wounds where there is no haemorrhage (and therefore no platelets). The clot (comprising fibrin, fibronectin, vitronectin, von Willibrand factor, thrombospondin) provides the provisional matrix for cellular migration. The platelets also contain dense bodies that store vasoactive

amines (e.g. serotonin) that increase microvascular permeability, leading to exudation of fluid into the extravascular space. **(**Enoch & Leaper, 2007)

2.1.2 Inflammation Phase

Inflammation can be divided into early and late phases depending on the time and duration of response and the type of inflammatory cell involved.

2.1.2.1 Early inflammatory phase (days 1–2) inflammation begins with the activation of the classical and alternative pathways of the complement cascade. This leads to infiltration of the wound with neutrophil granulocytes (polymorphonuclear leukocytes) that are attracted to the wound site within 24–48 hours of injury by a number of chemoattractants such as fragments of extracellular matrix protein, transforming growth factor-β, complement components (e.g. C3a, C5a).

2.1.2.2 Late inflammatory phase (days 2–3) on arriving at the wound site, blood monocytes undergo a phenotypic change to become tissue macrophages. Monocytes are attracted to the wound by a variety of chemoattractants including, complement, clotting components, fragments of immunoglobulin G, breakdown products of collagen and elastin, cytokines (e.g. leukotrine B4, platelet- derived growth factor, transforming growth factor-β).

Macrophages are the most important cells present in the later (48–72 hours) stages of the inflammatory process and appear to act as the key regulatory cells for repair. They function as phagocytic cells as well as being the primary producer of growth factors responsible for the proliferation and production of the extracellular matrix by fibroblasts, the proliferation of smooth muscle cells and endothelial cells resulting in angiogenesis.

Also, macrophages release proteolytic enzymes (e.g. collagenase) that help to debride the wound. If depleted, circulating monocytes and tissue macrophages cause severe alterations in wound healing, leading to poor debridement of the wound, delayed proliferation of fibroblasts, inadequate angiogenesis, and poor fibrosis. Additional growth factors (e.g. transforming growth factor-α, heparin-binding epidermal growth factor, basic fibroblast growth factor) are secreted by polymorphonuclear leukocytes and macrophages, which further stimulate the inflammatory response. During the late inflammatory phase, collagen fibres are

evident at the incision margins of the wound, but these are vertically oriented and do not bridge the incision. Epithelial cell proliferation continues, yielding a thickened epidermal covering layer. **(**Enoch & Leaper, 2007)

2.1.3 Proliferation (day 3 to week 2)

The proliferative phase starts at about day 3 and lasts for 2– 4 weeks after wounding and is characterized by fibroblast migration, deposition of the extracellular matrix and formation of granulation tissue. With progression of the proliferative phase, the provisional fibrin/fibronectin matrix is replaced by the newly formed granulation tissue. Epithelialization of the wound represents the final stage of the proliferative phase. **(**Enoch and Leaper, 2007)

Fibroblasts are attracted into the wound to synthesize granulation tissue. This granulation tissue is composed of procollagen, elastin, proteoglycans, and hyaluronic acid and forms a structural repair framework to allow vascular ingrowth. Myofibroblasts containing myofilaments (a-SMA, desmin) are responsible for physiologic wound contraction, and once a wound is closed, the immature scar can move on to the final maturation phase, which can last several months. (Wolfram, Tzankov, Pu lzl & Piza-Katzer, 2009)

2.1.4 Remodelling and scar maturation (week 1 to several weeks)

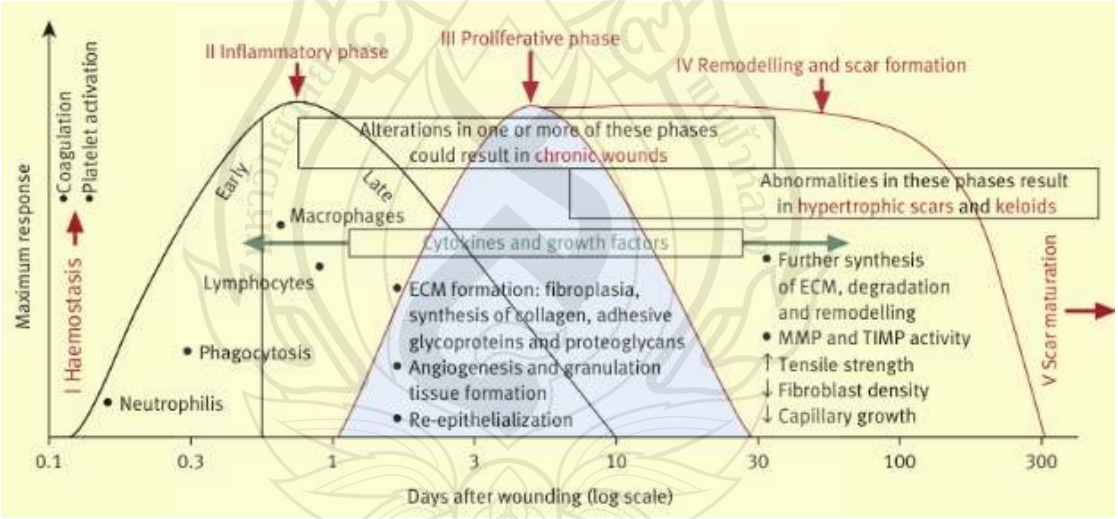
The synthesis and remodelling of the extracellular matrix is initiated concurrently with the development of granulation tissue and continues over prolonged periods. There is continuous synthesis and breakdown of collagen as the extracellular matrix is constantly remodelled, equilibrating to a steady state about 21 days after wounding. Wound contraction occurs through the interactions between fibroblasts and the surrounding extracellular matrix and is influenced by a number of cytokines including transforming growth factor-β, platelet-derived growth factor and basic fibroblast growth factor.

Collagen degradation is achieved by specific metalloproteinases that are produced by fibroblasts, neutrophils and macrophages at the wound site.

Metalloproteinases – the synthesis and secretion of metalloproteinases is regulated by growth factors, cytokines, and phagocytic stimuli. Metalloproteinases include interstitial collagenases which cleave the fibrillar collagen types I, II, and III,

gelatinases (or type-IV collagenases), which degrade amorphous collagen and fibronectin, stromelysins which catabolize a variety of constituents of the extracellular matrix including proteoglycans, laminin, fibronectin and amorphous collagen.

Metalloproteinases are dependent on zinc ions for their activity and should be distinguished from neutrophil elastase, cathepsin G, plasmin, and other serine proteases that can also degrade the extracellular matrix, but are not metalloenzymes. The activity of metalloproteinases is tightly regulated because they have the potential to degrade essential collagen and thereby cause impaired healing. They are typically elaborated as inactive (zymogen) precursors that must be first activated this is accomplished by certain proteases (e.g. plasmin) likely to be presentonly at injury sites. Also, activated collagenases can be rapidly inhibited by specific tissue inhibitors of metalloproteinases, produced by most mesenchymal cells. (Enoch & Leaper, 2007; Wolfram et al., 2009).



Source Enoch and Leaper (2007)

Figure 2.1 Phases of wound healing

2.2 Hypertrophic Scars and Keloids

Once the skin has been injured, normal healing involves the proliferation of fibrous ingrowth to repair the damaged tissues. When there is an excessive local tissue response to injury, a dysregulated deposition of extracellular matrix and collagen occurs resulting in either a hypertrophic scar or keloid. Both keloids and hypertrophic scars have a tendency to persist at the site of injury and recur after surgical excision. The distinction of what differentiates a hypertrophic scar from a keloid has been debated. (Thomas & Mobley, 2010)

2.2.1 Hypertrophic scars

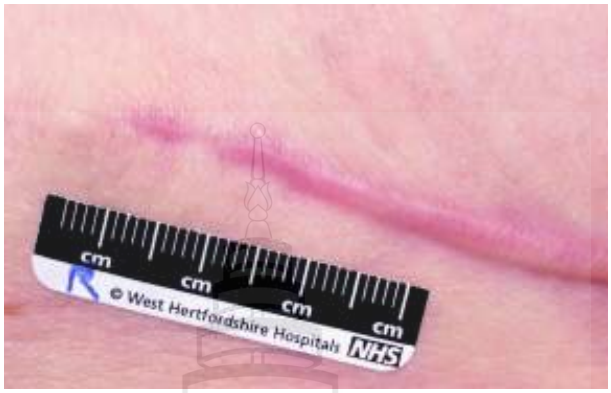
Hypertrophic scar usually occurs within 4 to 8 weeks following wound infection wound closure with excess tension or other traumatic skin injury, has a rapid growth phase for up to 6 months, and then gradually regresses over a period of a few years, eventually leading to flat scars with no further symptoms (Gauglitz et al,. 2011). Clinical include erythematous, raised, firm nodular growths that occur more commonly in areas subject to increased pressure or movement or in body sites that exhibit slow wound healing. The growth of hypertrophic scars is limited to the site of original tissue injury, unlike keloids, which proliferate beyond the boundaries of the initial wound.

2.2.2 Keloids

Keloid also persist, usually for long periods of time, and do not regress spontaneously. Keloids present as deep reddish purple papules and nodules, often on the earlobes, anterior chest, shoulders, and upper back. These lesions are more common in darker-skinned persons. (Sobanko & Alster, 2011).

Both lesions are commonly pruritic, but keloids may even be the source of significant pain and hyperesthesia In the majority of cases, hypertrophic scarring develops in wounds at anatomiclocations with high tension, such as shoulders, neck, presternum, knees and Ankles, whereas anterior chest, shoulders, earlobes, upper arms and cheeks have a higher predilection for keloid formation. Eyelids, cornea, palms, mucous membranes, genitalia and soles are generally less affected. Keloids

tend to recur following excision, whereas new hypertrophic scar formation is rare after excision of the original hypertrophic scar. (Gauglitz et al,. 2011)



Source Baker, Urso-Baiarda, Linge & Grobbelaar (2009)

Figure 2.2 Hypertrophic scar

Source Baker, Urso-Baiarda, Linge & Grobbelaar (2009)

Figure 2.3 Keloid

Histologically, both hypertrophic scars and keloids contain an overabundance of dermal collagen. Hypertrophic scars contain primarily type III collagen oriented parallel to the epidermal surface with abundant nodules containing myofibroblasts, large extracellular collagen filaments and plentiful acidic mucopolysaccharide. Keloid tissue, in contrast, is mostly composed of disorganized type I and III collagen, containing pale-staining hypocellular collagen bundles with no nodules or excess myofibroblasts. Both scar types demonstrate overproduction of multiple fibroblast proteins, including fibronectin, suggesting either pathological persistence of wound healing signals or a failure of the appropriate downregulation of wound-healing cells.

Table 2.1 Hypertrophic scars and keloids: epidemiological, clinical and histological differences.

	Hypertrophic scar	**Keloid**
Incidence	40% to 70% following surgery, up to 91% following burn injury	6% to 16% In African populations
Predilection sites	Shoulders, neck, pre sternum, knees and ankles	Anterior chest, shoulders, earlobes, upper arms and Cheeks
Time course	Within 4 to 8 weeks following wounding, rapid growth phase for up to 6 months, then regression over a period of a few years.	Within years after minor injuries or spontaneous formation on the mid chest in the absence of any known injury. Persistence for long periods of time. No spontaneous regression. High recurrence rates following excision
Appearance	Do not extend beyond the initial site of injury	Projects beyond the original wound margins

Table 2.1 (Continue)

	Hypertrophic scar	Keloid
Histological characteristics	Primarily fine, well-organized, wavy type III collagen bundles oriented parallel to epidermis surface with abundant nodules containing myofibroblasts and plentiful acidic mucopolysaccharide. Proliferating cell nuclear antigen (PCNA)/p53-level/ATP expression low	Disorganized, large, thick, type I and III hypocellular collagen bundles with no nodules or excess myofibroblasts. Poor vascularization with widely scattered dilated blood vessels. PCNA/p53-level/ATP expression high

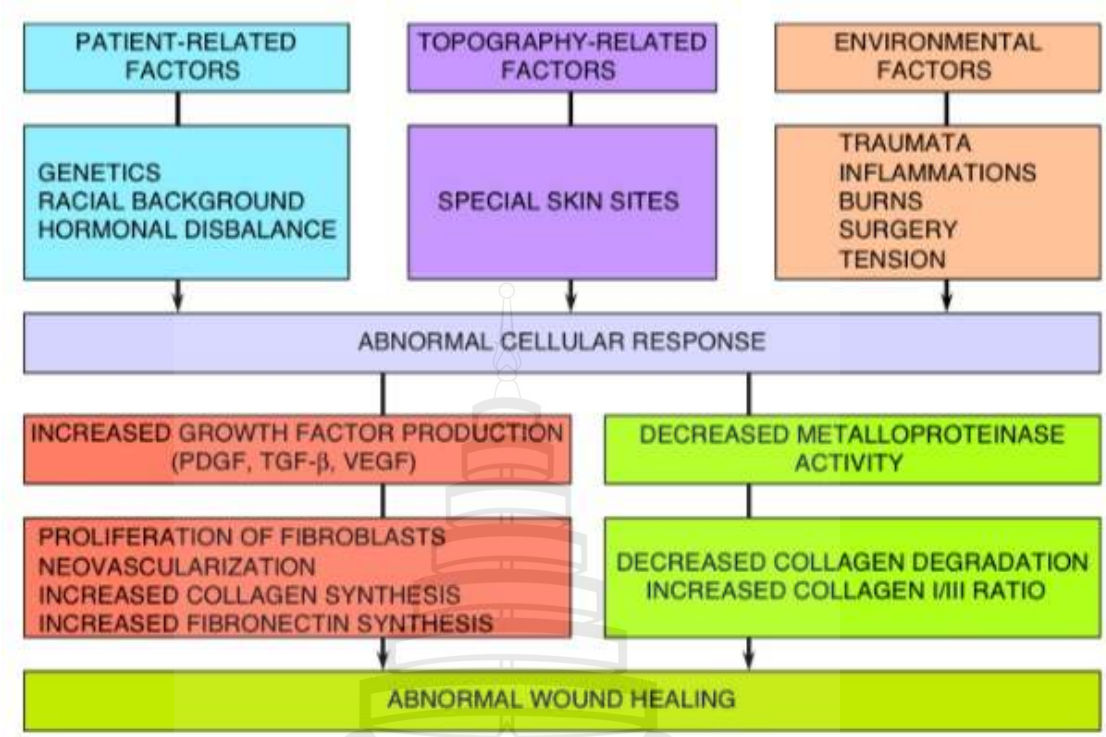
Source Gauglitz et al. (2011)

2.3 Pathophysiology of Hypertrophic Scars and Keloids

In the normal maturation phase, the nodularity and redness of the wound soften and flatten due to ongoing simultaneous collagen synthesis and degradation and the connective tissue elements regress after the third week. In keloids, the collagen synthesis is approximately 20 times as great as that in normal unscarred skin and three times as great as in hypertrophic scars. Abergel and colleagues showed that not only is collagen production high in hypertrophic scars and keloids, but the ratio of type I to type III collagen is also high (Abergel, Pizzurro & Meeker, 1985). Friedman and colleagues postulated that, in keloids, the downregulation of type I collagen synthesis is inefficient (Friedman, Boyd & Mackenzie, 1993). This collagen overproduction can be attributed to the stronger proliferating activity of keloid fibroblasts. Aside from high collagen synthesis and proliferation of fibroblasts in keloids, Oliver and colleagues found that keloid-derived fibroblasts show a rate of

fibronectin biosynthesis that is as much as four times as high as that of fibroblasts from normal scars and normal dermis (Oliver, Babu & Diegelmann, 1992).

Recent studies investigated the influence of various growth factors in scar and keloid formation. TGF-β and PDGF have been shown to play an integral role in the formation of hypertrophic scars and keloids. The majority of cells involved in wound healing express TGF-β in an inactive form that strongly promotes the chemotaxis of fibroblasts to the site of injury. Moreover, this growth factor plays a critical role in fibroblast proliferation and collagen production. When wound repair is completed, the activity of TGF-β is normally turned off. In keloidal tissue, TGF-β is overproduced and poorly regulated through normal autocrine signaling mechanisms. At the same time, keloid fibroblasts have greater numbers of growth factor receptors and respond more intensely to growth factors such as TGF-β and PDGF (Chen & Davidson, 2005). Less synthesis of molecules that promote matrix breakdown (e.g., MMPs) may also explain the lack of scar regression seen in keloids Furthermore, disturbed apoptosis mechanisms are discussed in the development of hypertrophic scars and keloids. Messadi and colleagues and Luo and colleagues demonstrated a significantly higher rate of apoptosis in normal skin fibroblasts than in keloidal fibroblasts. (Messadi, Le & Berg, 1999; Luo, Benathan & Raffoul, 2001; Wolfram et al., 2009)



Source Wolfram et al. (2009)

Figure 2.4 Pathogenesis of abnormal wound healing

2.4 Etiology

Factors that play a major role in keloid development are genetic predisposition and some form of skin trauma (English & Shenefelt, 1999). Skin or wound tension has also been implicated as a critical factor in hypertrophic scars and keloids, as have been incisions beyond the relaxed skin tension lines. Scars that cross joints or skin creases at a right angle are predisposed to form hypertrophic scars because of the constant tension forces that occur (Rudolph, 1987). Although keloids can occur at any age, they tend to develop more readily during and after puberty. Davies explained this fact by stating that younger individuals are more frequently subjected to trauma and their skin is more elastic than the skin of elderly persons (Davies, 1985). The fact that keloids are 15 times as likely to occur in darkerskinned individuals points to genetic

influences. Keloid formation mainly occurs in parts of the body with high concentrations of melanocytes, and it is rare on the soles and palms. Keloid formation has also been associated with endocrine factors. Menopause also prompts the recession of keloids, whereas women report keloid onset or enlargement during pregnancy. (Wolfram et al., 2009)

2.5 Treatment of Hypertrophic Scars and Keloids

2.5.1 Prevention

The most important factor in hypertrophic scar and keloid formation is prevention. Avoiding all unnecessary wounds, especially in keloid-prone patients, remains an obvious but imperfect solution. All surgical wounds should be closed with minimal tension, incisions should not cross joint spaces, midchest incisions should be avoided, and incisions should follow skin creases whenever possible. Especially in head and neck surgery, the esthetic subunits of the face must be considered for incision sites. An atraumatic operation technique should be used, followed by efficient hemostasis, and wound closure should include eversion of the wound edges. It is also crucial to properly debride contaminated wounds and limit foreign bodies in the form of polyfilamentous sutures. Particularly in the face, subcutaneous sutures should be used only when necessary. Furthermore, wound healing and the esthetic outcome of scar formation can be improved with massage or greasing ointments (Slemp & Kirschner, 2006; Baisch & Riedel, 2006; Wolfram et al., 2009)

2.5.2 Surgery

2.5.2.1 Surgery for Hypertrophic Scars

For patients with hypertrophic scars from complicated (e.g., infected) wounds or delayed closure, simple excision is the therapy of choice. Scar revision as a treatment achieves two aims excision and narrowing of scars as done for wide-spread scars and Z- or W-plasty designed to change the direction of the scar

2.5.2.2 Surgery for Keloids

Simple total excision of a keloid stimulates additional collagen synthesis, thus sometimes prompting quick recurrence of a keloid even larger than the initial

one. Surgical excision of a keloid alone is associated with a high recurrence rate. Thus, surgical therapy should be combined with adjuvant treatment such as pressure, corticosteroids, and radiotherapy. (Shaffer, Taylor & Cook-Bolden, 2002; Wolfram et al., 2009)

2.5.3 Pressure therapy

Pressure therapy has gained popularity for the management of hypertrophic scars and keloids since the 1970s. To date, pressure garments are frequently being used for the prevention of excessive scar formation post-burn (Gauglitz, 2013). However, their underlying mechanism of action remains poorly understood, but theories include the following

2.5.3.1 Decrease in blood flow with a resultant decrease in α2-macroglobulin and a subsequent increase in collagenase-mediated collagen breakdown, normally inhibited by α2-macroglobulin.

2.5.3.2 Hypoxia leading to fibroblast degeneration and collagen degradation.

2.5.3.3 Lower levels of chondroitin 4-sulfate, with a subsequent increase in collagen degradation.

2.5.3.4 Decreased scar hydration, resulting in mast cell stabilization and a subsequent decrease in neovascularization and matrix production.

Pressure therapy should be started immediately after reepithelialization of the wound, and patients should wear these pressure devices for continuous pressure (15–40 mmHg) 8 to 24 hours a day for the first 6 months of scar healing. The success rate depends largely on patient compliance. (Wolfram et al., 2009; Gauglitz et al., 2011)

2.5.4 Silicone based products

Silicone gel sheeting first reported in the early 1980s, silicone therapy has recently been marketed for at-home use to improve the appearance of any scar. It is recommended that these silicone sheets be worn at 12–24 hours per day over a period of 12–24 weeks beginning 2 weeks after wounding. (Gauglitz, 2013) The mechanism of action is unknown, but it has been suggested that the greater wound hydration achieved using occlusive therapy (silicone and non-silicone based) affects local keratinocytes to alter growth factor secretion and, secondarily, influences fibroblast regulation. (Chang, Kuo & Chiu, 1995; Fulton, 1995) It is also believed that hydration

decreases capillary permeability, inflammatory and mitogenic mediators, and collagen synthesis. (Wolfram et al., 2009) 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. Nevertheless, the current version of the international guidelines on scar management published in 2002 promotes silicone gel sheeting as first-line therapy for linear hypertrophic, widespread burn hypertrophic scars and minor keloids. (Gauglitz, 2013)

2.5.5 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. Radiation mediates its effects through inhibition of neovascular buds and proliferating fibroblasts, resulting in decreased collagen production. Side effects include hypo- and hyper-pigmentation, erythema, telangiectasia, and atrophy. (Brown & Pierce, 1986) 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. (Gauglitz, 2013).

2.5.6 Cryotherapy

Cryotherapy has been used as monotherapy and in conjunction with other forms of treatment for excessive scars. In particular, the combination of cryotherapy with intralesional TAC injections seems to yield marked improvement of hypertrophic scars and keloids. Recommend cryotherapy directly before the administration of intralesional TAC injections, because success rates seem to be increased with this sequence.

Cryotherapy is believed to induce vascular damage that may lead to anoxia and ultimately tissue necrosis. Success rates in studies in which contact or spray cryosurgery with liquid nitrogen was used varied between 32% and 74% after two or more sessions, with higher response rates of hypertrophic scars compared with keloids. The usefulness of cryotherapy, however, is limited to the management of small scars. A delay of several weeks between sessions is usually required for postoperative healing, and the commonly occurring side effects, including permanent hypo and hyperpigmentation, moderate skin atrophy, blistering and postoperative

pain, are major handicaps. Recently, the intralesional-needle cryoprobe method has been assessed in the treatment of hypertrophic scars and keloids, and has been demonstrated to have increased efficacy compared with that obtained with contact/ spray probes and shorter reepithelialization periods. (Gauglitz, 2013)

2.5.7 Laser therapy

Various lasers have been evaluated in the past decades for the improvement of hypertrophic scars and keloids. However, current data is difficult to compare due to the different laser settings utilized. The most encouraging results have been demonstrated with the pulsed dye laser (PDL), which was first described as promising for the treatment of younger hypertrophic scars and keloids.

Recently, the 1064-nm Neodym: YAG laser has been suggested as a promising means for the improvement of keloids and hypertrophic scars. Cho and colleagues found improvements of pigmentation, vascularity, pliability, and scar height in a small Korean patient population with keloids and hypertrophic scars after five to ten treatments (at 1–2-week intervals) using low fluences. Side-effects were mild and included a prickling sensation during treatmentand post-treatment erythema. (Akaishi et al., 2012; Cho, Lee, Lee, Lee, Bang & Oh, 2010)

Conventional CO_2 or Erbium: YAG lasers may be recommended for the ablation of inactive hypertrophic scars; their use for removal of keloids as monotherapy, however, should be avoided due to recurrence rates similar to that after excision of keloids. The combination with post-CO_2-laser steroid injections 3–4 weeks apart for a total of 6 months, however, seems to yield convincing results. Due to a lack of controlled studies, no statement can yet be made on the use of fractional CO_2 lasers in hypertrophic scars. (Gauglitz et al., 2011; Nast et al., 2012; Gauglitz, 2013)

2.5.8 Corticosteroids

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. 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. Response rates vary from 50% to 100%, and recurrence rates from 9% to 50%. Maximum dose in adults is 120 mg/treatment, or 20-40 mg/ lesion 1-2 cm^2. In children maximum dose, each treatment: 1-2 years of age 20 mg; 3-5 years of ages 40 mg; 6-10 years of age 80 mg. Adverse events include dermal atrophy, telangiectasia, and pain at the injection site. 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. Systemic complication (cushing syndrome) very rare with intralesional treatment (Gauglitz, 2013; Jalali & Bayat, 2007; Mustoe et al., 2002; Robles & Berg, 2007; Morris, 1972)

2.5.9 5-Fluorouracil

Intralesional injection of the pyrimidine analog 5-fluorouracil (5-FU) has been investigated for the regression of keloids and hypertrophic scars. 5-FU targets rapidly proliferating fibroblasts in dermal wounds responsible for excessive collagen production. Fitzpatrick was the first to report improved efficacy and less painful injections by mixing corticosteroids (triamcinolone acetonide) with 5-FU. This combined therapy provides also more rapid Response and fewer undesirable side effects than intralesional corticosteroid injection alone. (Wolfram et al., 2009)

2.5.10 Imiquimod 5% Cream

Imiquimod 5% cream, a topical immune response modifier, is approved for the treatment of genital warts, basal cell carcinoma, and actinic keratoses. Imiquimod stimulates interferon, a pro-inflammatory cytokine, which increases collagen breakdown. Additionally, imiquimod alters the expression of apoptosis-associated genes. It has been used in several trials, observational studies and case reports to reduce keloid recurrence after excisionand was reported to have positive effects on the recurrence rate of keloids. However, in a recent study reportpatients undergoing keloid excision and subsequent treatment with imiquimod 5% cream or placebo, no significant differences in 6-month keloid recurrence rates were detected between groups due to lack of statistical power. Thus additional studies may be necessary to

further characterize the ultimate success rates and the side effect profile. (Gauglitz, 2013; Zurada, Kriegel & Davis, 2006)

2.5.11 Onion Extract

Allium cepa, or onion extract, is found in numerous scar treatment products. It 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. A study by Chanprapaph and others suggested that these inhibitory effects may be mediated through inhibition of TGF-β1 and -β2 and SMAD proteins by quercetin. 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. (Chanprapaph, Tanrattanakorn, Wattanakrai, Wongkitisophon & Vachiramon, 2012; Jackson & Shelton, 1999; Chung, Kelley, Marra & Jiang, 2006; Gauglitz, 2013)

2.5.12 Interferons

Interferons are cytokines secreted by T-helper cells that, apart from other functions, suppress fibrosis. All interferon isoforms have been shown to reduce collagen and extracellular matrix production while increasing collagenase level but have been applied only experimentally and predominantly in small numbers of patients. Furthermore, the use of interferons is also associated with severe side effects, including fever, chills, night sweats, fatigue, myalgia, and headache. (Wolfram et al., 2009)

2.5.13 Bleomycin

Bleomycin sulfate is thought to inhibit collagen synthesis via decreased stimulation by TGF-β. Some studies demonstrate 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). Sporadically, development of depigmentation and dermal atrophy has been noted. Due to its toxicity, clinicians are encouraged to be aware of associated potential problems. Further investigation and efficacy trials are

necessary to include this agent in future treatment protocols. (Gauglitz, 2013; Espana, Solano and Quintanilla, 2001)

2.5.14 Botulinum toxin A (BTA)

BTA immobilizes local muscles, reduces skin tension caused by muscle pull, and thus, decreases microtrauma and subsequent inflammation. In a prospective, uncontrolled study intralesional injection with BTA has been proposed for the treatment of established demonstrated excellent clinical result by flattening of the lesions. Within the follow-up period of 1 year, no signs of recurrence were noted in any of the patients. In a recently published study objective evaluation of BTA-treated keloids using optical profilometry did not reveal any changes after BTA therapy compared with baseline. Also, no in-vitro effects of BTA on TGF-β subtypes or fibroblast proliferation could be found. So more in-depth studies on the effects of BTA on pathologic scars and/or mature keloids are needed before a comparatively expensive therapy for this particular indication can be postulated. (Gauglitz, 2013; Gauglitz, Bureik, Dombrowski, Pavicic, Ruzicka & Schauber, 2012)

2.5.15 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 signaling molecules such as tumor necrosis factor-α. PDT has been demonstrated to reduce type I collagen synthesis and fibroblast proliferation in vitro, which may be responsible for the improvement seen clinically. Recently study demonstrated 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. Also, when applied postoperatively after excision of keloids, no recurrence rates were seen at 9-month follow-up, with the exception of one patient. Based on this small amount of data available, PDT represents a promising, noninvasive treatment which produces a good cosmetic outcome with minimal side effects. However, more studies are needed to further evaluate the

optimal PDT treatment regime for this indication. (Gauglitz, 2013; Karrrer et al., 2003; Heckenkamp et al., 2004; Ud-Din et al., 2013)

2.6 Pulsed dye laser

Flashlamp pumped pulse dye laser (PDL) was developed in the mid-1980s to treat Port wine stain (PWS). This laser was developed to encompass the theory of selective photothermolysis. This theory states that a specific laser wavelength and energy be delivered to vaporize a specific target. The target was oxygenated hemoglobin in the red blood cell in the blood vessel. The most important factor was to keep the thermal damage within the blood vessel's 20–50-μm diameter through the use of a pulsed laser output of 350 μsec, which has been expanded to 450 μsec then 1500 μsec and now up to 40 ms. The original wavelength chosen was 577nm, which soon changed to 585nm and then 595nm to allow both deeper penetration as well as more efficient use of the excitation dye between the flashlamps of the laser. Finally, techniques providing epidermal cooling and copper vapor lasers emitting a wavelength of 577nm were also developed to target oxygenated hemoglobin. The use of a scanning hand-piece for use with non pulsed lasers was used to keep the laser energy within the thermal relaxation time of the blood vessel.

2.6.1 Selective Photothermolysis

2.6.1.1 Importance of Pulse Duration

To limit thermal damage to the intended target, the pulse duration must be shorter than the thermal relaxation time of the target tissue. The thermal relaxation time of tissue is defined as the time necessary for target tissue to cool down by 50% through transfer of its heat to surrounding tissue through thermal diffusion. If a targeted tissue can be heated sufficiently to affect it irreversibly before its surrounding tissue is damaged by thermal diffusion, selective photocoagulation occurs.

For vascular lesions, the exposure time should be long enough to conduct heat from the red blood cell (RBC) filled lumen to the entire blood vessel wall. The thermal relaxation time of vessels 10 to 50μm in diameter is 0.1 to 10ms, averaging 1.2ms. However, pulse durations less than 20μs result in vessel rupture and

hemorrhage secondary to RBC explosion. This will lead to hemosiderin pigmentation. Therefore, with single laser pulses, the therapeutic window is small. This argues for the development of a wider single pulse or a multipulsed laser that is able to transfer absorbed heat to the endothelium without causing its rupture.

2.6.1.2 Importance of Wavelength

The theory of selective photothermolysis is the basis for the development of the PDL with a wavelength of 577, 585 or 595nm to increase penetration into the dermis without loss of vascular specificity. Although blood absorbs 585-nm light about one-half as efficiently as it absorbs 577 nm light, 585-nm light will coagulate larger vessels better than 577-nm light at a given depth because of deeper penetration of laser energy. In addition, deeper vessels absorb laser energy at longer wavelengths. The tissue depth to which a given fluence will coagulate the target vessel depends largely on the blood volume of vessels above the target vessels. Superficial vessels containing blood will absorb laser light before it reaches deeper target vessels. This explains why multiple treatments are necessary.

Three manufacturers produce this type of laser. Candela Corporation (Wayland, MA) manufactures the SPTL line of machines, which originally emitted a wavelength of 585nm and now can emit wavelengths of 590, 595, and 600nm. The original pulse duration was 450μs and now can be increased to 40,000μs. The beam profile can be circular at 3, 5, 7, 10 and 12mm in diameter or elliptic at 2 x 7mm. Maximal energy fluences of 10 or 20J/cm^2 are available. The Candela machine uses cryogen spray cooling. Another PDL is the PhotoGenica V with a 585nm wavelength and the Photogenica V-Star with a 595nm wavelength and similar spot sizes and power as the Candela machine manufactured by Cynosure, Inc. (Chelmsford, MA). Currently produced Candela systems, according to their website, include the Vbeam (6 J output, 595-nm, 0.45- to 40-ms, with 5-, 7-, 10-, 3 x 10-mm handpieces) and Cbeam (6J output, 585-nm, 0.45-ms, 5-, 7-, 10-mm handpieces). Cynosure currently produces the PhotoGenica VStar (8 J output, 585- or 595-nm, 0.5- to 40-ms, with 7-, 10-, 12-mm and elliptical handpieces and PhotoGenica V (4J output, 585-nm, 0.45-ms, with 7- and 10-mm handpieces). Currently, no manufacturer produce a multi-wavelength dye laser. Both the Candela Sclerolaser and the Cynosure VLS multi wavelength systems have been discontinued, although they may be available on the used market. The Cynosure

PDL uses cold air cooling. The third company is DEKA (Florence, Italy), which produces the Dermobeam at 595nm with similar spot sizes and pulse durations as the other PDL. DEKA uses an integrated cooling system. The PDL beam profiles may be different between laser companies. With the Candela PDL a 10% to 20% overlapping spot provides for an even distribution of energy fluence. This is because of the Gaussian distribution of beam output. An 18% overlap has been found to cover the largest surface area with the least overlap. In contrast, the Cynosure PDL has a 'top hat' distribution of energy fluence. In addition, when the 5-mm-diameter spot size of the two lasers were tested, the Candela laser spot size was up to 35% larger than 5mm while the Cynosure laser was up to 8% smaller. Therefore it is prudent to check the diameter of the spot with burn paper before switching from one PDL machine to another. (Goldman, 2006)

2.6.2 Pulsed dye laser for treatment keloid and hypertrophic scar

Since the introduction of laser treatment for keloids in the mid-1980s, the therapeutic use of more and more lasers with different wavelengths has been investigated, and success has varied. Until today, the most encouraging results have been obtained with the 585-nm pulsed-dye laser (PDL), which has been recognized as an excellent therapeutic option for the treatment of younger hypertrophic scars and primarily keloids. pulsed dye laser has shown limited promise, with a 57 to 83 percent improvement rate.(Juckett and Hartman-Adams, 2009) Non overlapping laser pulses at fluences ranging from 6.0 to 7.5 J/cm^2 (7-mm spot) or from 4.5 to 5.5 J/cm^2 (10-mm spot) have been recommended for the treatment of hypertrophic scars and keloids. Two to six treatments may be necessary to successfully improve scar resolution, including scar color, height, pliability and texture (Gauglitz et al., 2011)

2.6.2.1 Mechanism

It is thought that the PDL improves keloids or hypertrophic scars by inducing capillary destruction, which generates hypoxemia and in turn alters local collagen production. Also, increased production of MMPs (eg, collagenase) has been described upon PDL treatment. The PDL has been demonstrated to reduce expression of transforming growth factor β, fibroblastproliferation, and collagen type III deposition. Other possible explanations include released mast cell constituents (such as histamine and interleukins) that could affect collagen metabolism, and the heating

of collagen fibers and breaking of disulfide bonds with subsequent collagen realignment. (Sobanko & Alster, 2011; Gauglitz, 2013; Wolfram et al., 2009)

2.6.2.2 Complication and Post-procedure care

It is normal for patients to experience redness and swelling in the treated area immediately following treatment. This will usually go away over the next few days. Some bruising (purpura) is not uncommon with more aggressive energy levels. Such bruising fades, as does any bruise, usually over a week or so, with more intense therapies sometimes taking longer. Following treatment, cold packs are used to help decrease swelling and to help with discomfort. Permanent side-effects of pulsed dye laser therapy are rare. Scarring is described it is typically focal and resembles a chicken-pox scar. The risk is in the order of 1 in 1,000 patients. Some degree of difference between treated and untreated areas is not uncommon. Patients presenting with rosacea, but who also have background sun-induced redness, may wish to consider treatment to the whole 'unit' of the skin, such as the cheek, or even whole-face therapy if this seems to be indicated. Crusting, scabbing and blistering may occur at high energy levels. Such crusting can be treated with a heavy moisturiser, or even a coating of Vaseline, and settles over one week. Secondary infection is a very rare side-effect of pulsed dye laser therapy.

A topical healing ointment under a nonstick bandage can be applied for the first few postoperative days to protect the skin. Treated areas should be gently cleansed daily with water and mild soap. Strict sun avoidance and photoprotection should be advocated between treatment sessions to reduce the risk of pigment alteration. Hyperpigmentation has been reported with varying frequencies (1%–24%). Topical bleaching agents (such as hydroquinone or kojic acid) may be applied to hasten pigment resolution. (Sobanko & Alster, 2011; Bhatt & Alster, 2008; Alster, 2002; Manuskiatti & Fitzpatrick, 2002; Hermanns et al., 2001)

2.6.3 Studies about the efficacy of pulsed dye laser for the treatment of hypertrophic Scars and keloids.

Alster (1994) reported an average improvement of 57% after the first treatment and 83% after the second treatment with PDL for hypertrophic surgical and traumatic scars. In addition to a reduction in erythema, flattening, a clear reduction in

itching and pain, and optimization of the skin texture have been observed. The entire scar in each patient was exposed to PDL at a wavelength of 585 nm, a pulse duration of 0.45 ms, and a fluence of 6.5 to 7.25 J/cm2.

Kuo YR et al., (2005) Study in keloid tissues from 10 patients with intra-lesional or punch biopsies before and 7 days after PDL treatments the investigation show that PDL treatments can decrease transforming growth factor-beta1 (TGF-beta1)-induction and up-regulation of matrix metalloproteinase (MMP) expression in keloid. So auther suggest that PDL treatment can alters signaling pathways to favor collagen degradation and fibroblast apoptosis.

Manuskiatti, Wanitphakdeedecha & Fitzpatrick (2007) investigate the effect of pulse width of 595-nm PDL in treating keloidal and hypertrophic scars. On each of 19 patients, keloidal or hypertrophic median sternotomy scars were divided into two segments. Both segments on all patients were randomly treated with a 595-nm PDL at a fluence of 7 J/cm2 and pulse widths of 0.45 and 40 ms to both segments, every 4 weeks for a total of three treatments. The volume of segments treated with 0.45- and 40-ms pulses decreased significantly after two treatments. Segments treated with a 0.45-ms pulse width showed significantly greater improvement than those treated with 40-ms pulses after three treatments. Elasticity of 0.45-ms segments was significantly higher than those of 40-ms segments, following two treatments. Pulse width had no significant effect in improvement of scar erythema.

Yang et al., (2012) study the Effect of flashlamp pulsed dye laser on the expression of connective tissue growth factor (CTGF) in Keloids. Three sessions of PDL treatment, with pulse duration of 1.5 milliseconds, spot size 7 mm, duration 20 milliseconds/delay 10 milliseconds and fluence of 10 J/cm2, were performed on the keloids at 3- to 4-week intervals. Punch biopsies were performed both on the treated and untreated keloids prior to the first treatment and after the final treatment. The specimens underwent realtime polymerase chain reaction (PCR) and immunohistochemistry (IHC) to investigate the CTGF mRNA and protein expression after PDL treatment. The Results show that the CTGF mRNA was significantly down-regulated after PDL treatment in 80.77% of patients as compared to the control group. IHC investigation showed that after treatment the CTGF positive cells also significantly decreased in number as compared to the control group in 80.77% of

patients. Using the Vancouver scar scale (VSS), there was an average decrease of 20.85 +/- 12.33% after PDL treatment.

Connell & Harland study the treatment of keloid scars with pulsed dye laser and intralesional steroid. Keloid scars of 10 patients were managed with a combined treatment modality of pulsed dye laser (PDL) and intralesional steroid. Results show seven of the patients benefited in terms of the raised nature of the scars being improved by 60%, erythema improved by 40%, and pain/itching by 75%. Three of the patients, who had presternal scars, had no benefit.

Elwakil (2009) study the pulsed dye laser with corticosteroid injections for treatment of hypertrophic scars twelve patients presented with hypertrophic scars of a duration $\geq$ 6 months were treated by combined pulsed dye laser and intralesional triamcinolone acetonamide (TAC) injections of (40mg/mL). Treatment was repeated at 4 weeks intervals till the objective goal was obtained or no further improvement could be achieved. pulsed dye laser parameters was setting at a fluence of 5-7 J/cm2, pulse duration of 450μsec and spot sizes of 5 and 7mm, were used. Treatment was carried out with pulses overlapping of up to 10%. Follow by intralesional triamcinolone TAC injections of (40mg/mL) in a total dose/injection of up to 40mg were carried out. The result at 6 months period of follow up after treatment including the improvement of the subjective symptoms, scars' pliability scale, erythema analysis and scars' dimensions. The percentages of erythema clearance after treatment were found to be 62%±12.53% at statistical significances of $p \leq 0.01$ hyperpigmentation was elicited in 5 scars (38.46%) and hypopigmentation and dermal atrophy were observed in 2 scars (15.38%).

Several reports have shown a trend toward better clinical improvement using low to moderate fluences, But there's no study compare the clinical improvement and side effect of the combination of 595-nm pulsed dye laser and intralesional corticosteroid injections versus intralesional corticosteroid injections alone. We hypothesize that this combination may have a synergistic effect on keloid and hypertrophic scars and obtain the better clinical outcomes. Therefore, the purpose of this study is to compare the clinical improvement and side effect of the combination of pulsed dye laser and intralesional corticosteroid injections versus intralesional corticosteroid injections alone for the treatment of keloid and hypertrophic scar.

CHAPTER 3

RESEARCH METHODOLOGY

3.1 Study Design

A randomized, Single-blind, clinical controlled trial comparison study.

3.2 Study Population

Thai patients, ages 18–55 years old with keloid and hypertrophic scars.

3.3 Sample

Thai patients, ages 18–55 years old, with keloid and hypertrophic scars who want to treat their scars at Mae Fah Luang University Hospital, Bangkok.

3.4 Sample Size Determination

The sample size was calculated from the formula of one sample, using the ratio of measurement from the previous study (Elwakil, 2009). From the formula

$$n = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \, \sigma^2}{d^2}$$

n = sample size

Assign $\alpha = 0.05$, $Z_{\alpha/2}$ = 95% confidence interval =1.96

$\beta = 0.1$, $Z_{\beta} = 1.28$

$\sigma^2 = (SD_1+SD_2)^2 = (2.13+1.06)^2 = 5.008$

$$n = 5\,\frac{(1.96+1.28)^2}{2^2} = 13$$

A drop-out rate of 20% was expected, so sixteen patients (n = 16) were recruited.

3.5 Selection Criteria

3.5.1 Inclusion Criteria

3.5.1.1 Healthy Thai patients with keloid and hypertrophic scar of at least 6-month duration.

3.5.1.2 The lesions had to be a minimum of 20 mm in length.

3.5.1.3 The lesions had not received prior treatment before.

3.5.1.3 Both males and females, ages 15-55 years old.

3.5.1.4 All subjects were able to participate in the treatment once a month for the duration of three months and could be followed up at one month after the last treatment.

3.5.1.5 All female of child-bearing potential had an acceptable form of birth control during the study.

3.5.1.6 All subjects were required to sign an informed consent form of benefits, risks and possible complications of the treatment and publication of photographs.

3.5.2 Exclusion Criteria

3.5.2.1 Pregnancy and lactation

3.5.2.2 Patients planning pregnancy in the near future.

3.5.2.3 Medical illnesses such as hypertension or any other serious cardiac disease.

3.5.2.4 Previous history of triamcinolone hypersensitivity.

3.5.2.5 Infection, inflammation or tattoo in the treatment areas.

3.5.2.6 Use of any topically or oral photosensitizing drugs within 6 month prior to entry into the study.

3.5.3 Discontinuation Criteria

3.5.3.1 Participants who have serious complications (severe burning and secondary infection) and they will receive an appropriate treatment.

3.5.3.2 Participants who could not attend the treatment visits.

3.5.3.3 Participants who provide other treatment of scars during the study.

3.5.3.4 Participants who pregnancy.

3.6 Study Location

Mae Fah Luang University Hospital, Bangkok.

3.7 Tools and Materials

3.7.1 Registration form

3.7.2 Research procedure line

3.7.3 Informed consent

3.7.4 Digital camera Canon PowerShot G12 (Canon Inc., Tokyo, Japan)

3.7.5 Caliper

3.7.6 Mexameter MX 18

3.7.7 Cutometer MPA 580

3.7.8 Pulsed dye laser (595-nm V beam; Candela, USA)

3.7.9 Triamcinolone acetonide (40mg/mL)

3.7.10 A record of research result

3.7.11 A record of side effect of treatment

3.7.12 A record of patient satisfaction

Figure 3.1 Pulsed dye laser (595-nm V beam; Candela, USA)

3.8 Intervention

Half of the patient's scars was treated with the combination of pulsed dye laser (595nm V beam; Candela, USA) and intralesional corticosteroid injections (triamcinolone acetonide 40mg/mL) and another half with intralesional corticosteroid injections alone (triamcinolone acetonide 40mg/mL).

3.9 Study Procedures

3.9.1 Patients were selected to enroll in the study according to the selection criteria.

3.9.2 The researcher intensively explained the purpose of the research, process during the study, benefits and possible complications of the treatment.

3.9.3 The patients signed an informed consent form for participation in the study.

3.9.4 The information of the patient was recorded.

3.9.5 The measured area was mapped with a permanent marker on a flexible transparent sheet using natural landmarks such as lentigines or moles as referenced landmarks.

3.9.6 Before each treatment at week 0, 4, 8, 12. Photography was obtained using digital camera Canon PowerShot G12 (Canon Inc., Tokyo, Japan). Lens aperture, exposure time, subject distance and room illumination were kept constant.

3.9.7 Measure and record scars' dimensions (height length width) by caliper at week 0, 4, 8, 12.

3.9.8 Measure and record scars' erythema by mexameter MX 18 at week 0, 4, 8, 12.

3.9.9 Measure and record scars' pliability by Cutometer MPA 580 at week 0, 4, 8, 12.

3.9.10 The scars of each subject was divided into two segments and randomly treated with the combination of pulsed dye laser and intralesional corticosteroid injections (TAC+PDL) to half of the scars and intralesional corticosteroid injections alone (TAC) to the other half in Figure 3.2.

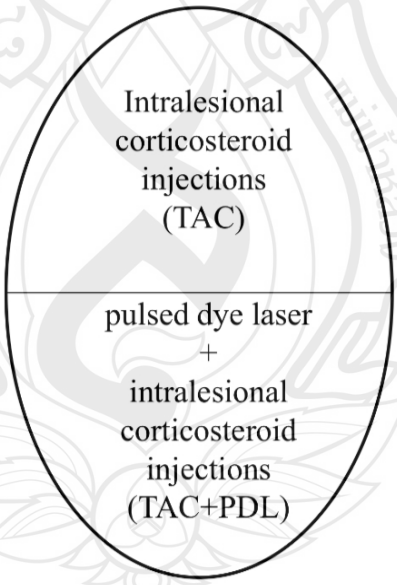


Figure 3.2 The scars was divided into two segments. The half of scars segment was treated with the combination of pulsed dye laser and intralesional corticosteroid injections (TAC+PDL) and the other half was treated with intralesional corticosteroid injections alone (TAC).

3.9.11 The researcher generated randomization sequence which randomly determined which side of the patient's scars to be treated with the combination of pulsed dye laser and intralesional corticosteroid injections and intralesional corticosteroid injections alone by using "Random Allocation Software" and conceals the sequence in opaque envelopes.

3.9.12 The patient selected the randomization sequence envelop.

3.9.13 Before treatment, all laser safety measures were done. PDL (595nm v beam; Candela,USA), at a fluence of 5-7 J/cm^2, pulse duration of 450 μsec and spot sizes of 7mm, were used. Treatment was carried out with non-overlapping laser pulses at the side of combination treatment. Epidermal cooling was achieved by means of a cryogen spray cooling (CSC) device. The CSC device was fixed to spurt duration of 30 ms with a delay of 30 ms.

3.9.14 After PDL, concomitant triamcinolone acetonide injections (TAC) of 40mg/mL diluted with xylocain 1:1 were injected into the body of the keloid and hypertrophic scars using a 30- gauge needle until slight blanching was clinically visible and not exceed 0.5 mL per 1 cm^2 of the lesion. The delivered dose was adjusted according to the extent of the lesions but did not exceed 6 mL per session.

3.9.15 After treatment, an antibacterial ointment (2% Mupirocin ointment, Bacidal®, Charoon Bhesaj LTD., Thailand) was applied to the treated area.

3.9.16 The researcher evaluated the patients during and post-treatment about their discomfort (Pain and burning sensation), erythema, brusing, edema, crusting and other side effects.

3.9.17 Subjects were instructed to cleanse the treated sites gently with tap water and shower soap and to reapply mupirocin ointment twice a day until all bruises or crusting had subsided.

3.9.18 Subjects were also asked to avoid sun exposure, which could cause hyperpigmentation.

3.9.19 Advise if the patients experienced any severe side effects, they had to go to see the researcher before the next treatment session. The researcher would treat the side effects.

3.9.20 The treatment was done once a month for three months consecutively. The treatment each side of the scars was the same in all the three treatment sessions.

3.10 Follow Up

Follow up at week 4, 8, 12, the researcher took a photograph and measure scars' dimensions, scars' erythema, scars' pliability and side effect of each patient every visit.

3.11 Outcome Measurement and Data Collection

3.11.1 Clinical Evaluation

Improvement of scars' dimensions (height length width), pliability, erythema evaluated and analyze the data by statistical methods.

3.11.2 Patient Assessments

Patients were asked to evaluate the improvement of scars at week 12 using the grading scales: 0 = no improvement, 1= <25% (mild) improvement, 2= 25-50% (moderate) improvement, 3= 51-75% (good) improvement, 4= >75% (excellent) improvement.

3.11.3 Measurement of Side Effects

On each follow-up visit, the presence of adverse effects including hypopigmentation, hyperpigmentation, telangiectasia and textural changes (epidermal atrophy) were assessed as follows: 0 = absent; 1 = occur.

3.12 Data Analysis

Data are presented as numbers, percentages, mean values ± standard deviations. Results were statistically analyzed and statistical significance was set at $p \leq 0.05$

3.12.1 Qualitative Data

3.12.1.1 Demographic data is calculated and displayed in number and percentages.

3.12.1.2 Side effect of treatment use the descriptive statistics and summary information in the form of percentages.

3.12.2 Quantitative Data

3.12.2.1 Age in the form of mean and standard deviation.

3.12.2.2 Number and location of scar are presented as numbers (%),

3.12.2.3 Scars duration (months) are presented as numbers (%), mean values ± standard deviations.

3.12.2.4 Scars' dimensions (height length width), pliability, erythema evaluated data at weeks 0, 4, 8, 12 of both groups. Data are presented as numbers, mean values ± standard deviations and ranges and compare improvements of week 0 to each follow-up visit with paired t-test (if the data are normal distribution) or Wilcoxon Match Pair sign rank test (if the data are not normal distribution).

3.12.2.5 Comparison the mean difference of scars' dimensions (height length width), pliability, erythema of each session and baseline (week0) of two groups with paired t-test (if the data are normal distribution) or Wilcoxon Match Pair sign rank test (if the data are not normal distribution).

3.12.2.6 The improvement of scars that evaluated by three independent dermatologists, the information reported in the form of mean and standard deviation and compare the data between two groups with paired t-test (if the data are normal distribution) or Wilcoxon Match Pair sign rank test (if the data are not normal distribution).

3.12.2.7 The improvement of scars that evaluated by patient, the information reported in the form of mean and standard deviation and compare the data between two group with paired t-test (if the data are normal distribution) or Wilcoxon Match Pair sign rank test (if the data are not normal distribution).

CHAPTER 4

RESULTS

The study design was a randomized, Single-blind, Clinical controlled trial comparison study. The study was initiated under a hypothesis that the combination of pulsed dye laser and intralesional corticosteroid injections has higher efficacy and lower side effect than intralesional corticosteroid injections alone for treatment of keloid and hypertrophic scars. The results from the study are categorized into demography, clinical evaluation, patient's satisfaction and side effect.

4.1 Demography

Sixteen healthy volunteers and sixteen patients with a diagnosis of keloid and hypertrophic scars were recruited from the outpatient department (OPD), Mae Fah Luang University Hospital. The diagnosis of keloid and hypertrophic scars is based on clinical features by dermatologist.

Table 4.1 Demography

Clinical data	All patient
Sex	
Male	11
Female	5
Age (Years)	
(Mean±SD)	25.06 ± 6.98
(Min-Max)	15-44

Table 4.1 (Continue)

Clinical data	All patient
Skin photo type	
III	3
IV	10
V	3
Scar duration	
(Mean±SD)	9.75 ± 5.09
(Min-Max)	2-24
Location	
Head & neck	1
Trunk	7
Extremities	8
Occupation	
Business owner	2
Modeling	1
Officer	10
Student	3
Underlying disease	
None	16

During a study period, a total of 16 participants were complete studied. The mean age of patients was 25.06 ± 6.98 years (range, 15-44 years). The mean duration of keloid and hypertrophic scar was 9.75 ± 5.09 years. Most of the subjects had Fitzpatrick skin type IV 10 person, the others were type IIII and V 3person, for each. Most of scars located at extremities 8 person, the others were trunk 7 person and head & neck 1 person.

4.2 Clinical Evaluation

Among sixteen subjects had completed the three sessions of treatments. The scar of each was divided into 2 groups. Groups I was treated with intralesional corticosteroid injections alone. Groups II was treated with intralesional corticosteroid injections and pulsed dye laser.

4.2.1 Scar's Height

Scar's height was evaluated by Caliper before treatment and at weeks 4 8 12. Data is shown in table 4.2.

Table 4.2 Scar's Height (mm)

Subject	Group I (TAC)				Group II (TAC+PDL)			
	Baseline	**Wk 4**	**Wk 8**	**Wk 12**	**Baseline**	**Wk 4**	**Wk 8**	**Wk 12**
1	3.90	3.76	2.43	1.77	3.30	3.22	2.36	1.78
2	5.02	4.86	2.15	1.63	5.44	5.29	1.79	0.97
3	3.20	3.14	1.97	1.56	3.10	3.20	1.18	1.03
4	6.12	5.88	4.54	2.50	6.12	5.95	4.63	1.25
5	7.34	7.18	5.87	3.94	8.56	8.38	3.55	1.54
6	4.47	4.95	1.58	1.48	5.25	4.77	1.57	0.87
7	6.36	5.67	3.85	0.54	6.22	6.21	3.05	1.74
8	4.30	4.79	2.88	1.67	4.10	3.89	2.23	0.94
9	8.44	7.35	3.57	2.12	7.98	7.88	5.85	2.86
10	5.67	5.58	2.04	0.80	5.65	5.49	3.69	2.59
11	4.33	4.08	3.02	2.60	4.59	4.44	2.53	2.07
12	6.55	6.38	2.45	1.78	6.78	6.67	1.34	1.21
13	5.33	5.09	2.66	1.66	5.40	5.34	2.08	1.77
14	7.34	7.19	3.23	2.05	6.04	5.85	2.49	0.88
15	3.46	3.33	2.04	1.98	3.25	3.66	1.76	0.77
16	4.46	4.11	1.09	0.79	5.35	5.57	2.34	0.67

Table 4.3 Scar's height in the segments was treated with intralesional corticosteroid injections alone (groups I) in each treatment sessions (n=16).

Duration	Mean (mm)	SD	Min	Max
Baseline	5.39	1.52	3.20	8.44
Wk 4	5.21	1.35	3.14	7.35
Wk 8	2.84	1.19	0.58	4.54
Wk 12	1.84	0.76	0.48	2.12

Table 4.3 Reports Scar's height of groups I in Mean, Standard deviation, Minimum and Maximum value in each sessions of treatment. Scar's height at baseline, weeks 4 8 and 12 were 5.39±1.52, 5.21±1.35, 2.84±1.19 and 1.84±0.76 respectively. Mean scar's height was decreased in every treatment sessions.

Table 4.4 Scar's height in the segments was treated with intralesional corticosteroid injections and pulsed dye laser (groups II) in each treatment sessions (n=16).

Duration	Mean (mm)	SD	Min	Max
Baseline	5.45	1.57	3.10	8.56
Wk 4	5.36	1.51	3.20	8.38
Wk 8	2.65	1.25	1.18	4.63
Wk 12	1.43	0.66	0.60	1.77

Table 4.4 Reports Scar's height of groups II in Mean, Standard deviation, Minimum and Maximum value in each sessions of treatment. Scar's height at baseline, weeks 4 8 and 12 were 5.45±1.57, 5.36±1.51, 2.65±1.25 and 1.43±0.66 respectively. Mean scar's height was decreased in every treatment sessions.

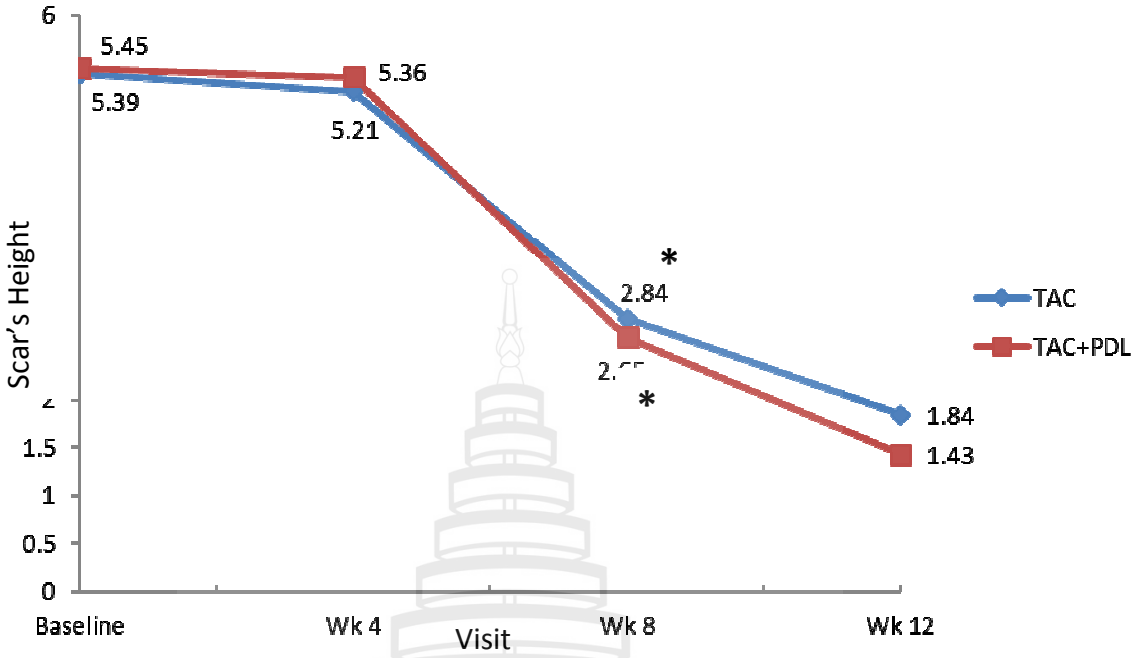


Figure 4.1 Mean scar's height of both groups in each treatment sessions

Figure 4.1 presents the mean scar's height of both groups in each treatment sessions. Mean scar's height of both groups was decreased in every treatment sessions. And after 2 treatment mean scar's height in both groups was decreased significantly (p<0.001) when compare with baseline (*).

Table 4.5 Comparison the mean scar's height between baseline and each treatment sessions in segments was treated with intralesional corticosteroid injections alone (groups I).

Duration	Mean±SD (mm)	Paired Difference	*p*-value
Baseline – Wk 4	5.39±1.52	0.18±0.37	0.064
	5.21±1.35		
Baseline – Wk 8	5.39±1.52	2.55±1.19	<0.001
	2.84±1.19		
Baseline – Wk 12	5.39±1.52	3.55±1.44	<0.001
	1.84±0.76		

Note. Mean scar's height between baseline and each treatment session was compared using paired t-test, p value < 0.05 denote significant difference.

Table 4.5 Comparison the mean scar's height between baseline and each treatment sessions in segments was treated with intralesional corticosteroid injections alone.

After the first treatment (Weeks 4): There was no significant difference between mean scar's height at baseline (5.39 ± 1.52) and weeks 4 (5.21 ± 1.35) (p = 0.064). The mean difference between two groups was 0.18. The difference in mean scar's height between baseline and weeks 4 did not reach significance (p = 0.064).

After the second treatment (Weeks 8): The mean scar's height at weeks 8 (2.84±1.19) was significantly lower than baseline (5.39 ± 1.52) (p < 0.001). The mean difference between two groups was 2.55. The scar's height at weeks 8 was reduced form baseline significantly (p < 0.001).

After the third treatment (Weeks 12): The mean scar's height at weeks 12 (1.84±0.76) was significantly lower than baseline (5.39 ± 1.52) (p < 0.001). The mean difference between two groups was 3.55. The scar's height at weeks 12 was reduced form baseline significantly (p < 0.001).

Table 4.6 Comparison the mean scar's height between baseline and each treatment sessions in segments was treated with intralesional corticosteroid injections and pulsed dye laser (groups II).

Duration	Mean±SD (mm)	Paired Difference	*p*-value
Baseline – Wk 4	5.45±1.57	0.08±0.20	0.120
	5.36±1.51		
Baseline – Wk 8	5.45±1.57	2.79±1.28	<0.001
	2.65±1.26		
Baseline – Wk 12	5.45±1.57	4.01±1.46	<0.001
	1.43±0.66		

Note. Mean scar's height between baseline and each treatment sessions was compared using paired t-test, p value < 0.05 denote significant difference.

Table 4.6 Comparison the mean scar's height between baseline and each treatment sessions in segments was treated with intralesional corticosteroid injections and pulsed dye laser.

After the first treatment (Weeks 4) : There was no significant difference between mean scar's height at baseline (5.45 ± 1.57) and weeks 4 (5.36 ± 1.51) (p = 0.12). The mean difference between two groups was 0.08. The difference in mean scar's height between baseline and weeks 4 did not reach significance (p = 0.12).

After the second treatment (Weeks 8): The mean scar's height at weeks 8 (2.65±1.26) was significantly lower than baseline (5.45 ± 1.57) (p < 0.001). The mean difference between two groups was 2.79. The scar's height at weeks 8 was reduced form baseline significantly (p < 0.001).

After the third treatment (Weeks 12): The mean scar's height at weeks 12 (1.43±0.66) was significantly lower than baseline (5.45 ± 1.57) (p < 0.001). The mean difference between two groups was 4.01. The scar's height at weeks 12 was reduced form baseline significantly (p < 0.001).

Table 4.7 Comparison the difference of mean scar's height in each treatment sessions between groups I and groups II.

Difference of Mean Height	Group I (TAC)	Group II (TAC + PDL)	Paired Differences	*p*-value
Baseline – Wk 4	0.18±0.37	0.08±0.20	0.10±0.48	0.405
Baseline – Wk 8	2.95±1.39	3.12±1.30	-0.24±1.36	0.449
Baseline – Wk 12	3.76±1.57	4.26±1.41	-0.46±1.26	0.165

Note. The difference of mean scar's height in each treatment sessions between groups I and groups II was compared using paired t-test, p value < 0.05 denote significant difference.

Table 4.7 Comparison the difference of mean scar's height in each treatment sessions between groups I and groups II.

After the first treatment (Weeks 4): There was no significant difference between the reduction of mean scar's height in groups I (0.18 ± 0.37) and groups II (0.08 ± 0.2) (p = 0.405). The mean difference between two groups was 0.1. The reduction of mean scar's height between groups I and groups II at weeks 4 did not reach significance (p = 0.405).

After the second treatment (Weeks 8): There was no significant difference between the reduction of mean scar's height in groups I (2.95 ± 1.39) and groups II (3.12 ± 1.3) (p = 0.449). The mean difference between two groups was 0.24. The reduction of mean scar's height between groups I and groups II at weeks 8 did not reach significance (p = 0.449).

After the third treatment (Weeks 12): There was no significant difference between the reduction of mean scar's height in groups I (3.76±1.57) and groups II (4.26±1.41) (p = 0.165). The mean difference between two groups was 0.46. The

reduction of mean scar's height between groups I and groups II at weeks 12 did not reach significance ($p = 0.165$).

4.2.2 Scar's length

Scar's length was evaluated by Caliper before treatment and at weeks 4 8 12. Data is shown in table 4.8.

Table 4.8 Scar's length (mm)

Subject	Group I (TAC)				Group II (TAC+PDL)			
	Baseline	**Wk 4**	**Wk 8**	**Wk 12**	**Baseline**	**Wk 4**	**Wk 8**	**Wk 12**
1	50.21	50.46	50.37	50.22	45.56	45.62	45.66	45.61
2	20.45	19.76	19.41	19.39	19.78	19.68	19.61	19.19
3	15.44	15.37	15.62	15.88	17.78	17.31	17.45	17.23
4	12.54	12.34	12.18	12.29	13.47	13.23	13.16	13.07
5	13.27	13.38	13.09	12.66	14.03	13.75	13.62	13.55
6	6.33	6.25	6.79	6.98	6.56	6.65	6.83	6.94
7	7.42	7.32	7.31	7.12	6.22	6.53	5.76	5.87
8	20.39	20.43	20.14	20.08	18.45	18.4	18.67	18.32
9	17.46	17.67	17.78	17.76	18.47	18.33	18.31	18.28
10	11.22	11.45	11.08	11.02	14.53	14.37	14.29	14.24
11	16.56	16.45	16.72	16.75	15.77	15.45	15.34	15.57
12	20.35	20.55	19.53	19.72	20.49	20.56	20.66	20.87
13	13.79	13.54	13.27	13.11	12.58	12.15	12.25	12.18
14	25.69	25.67	25.16	25.11	23.67	23.51	23.67	23.56
15	17.56	17.88	17.38	17.29	16.34	16.58	16.81	16.74
16	11.45	11.25	11.13	11.12	11.65	11.45	11.33	11.28

Table 4.9 Scar's length in the segments was treated with intralesional corticosteroid injections alone (groups I) in each treatment sessions (n=16).

Duration	Mean (mm)	SD	Min	Max
Baseline	17.51	10.09	6.33	50.21
Wk 4	17.49	10.16	6.25	50.46
Wk 8	17.31	10.08	6.79	50.37
Wk 12	17.28	10.06	6.98	50.22

Table 4.9 Reports Scar's length of groups I in Mean, Standard deviation, Minimum and Maximum value in each sessions of treatment. Scar's length at baseline, weeks 4 8 and 12 were 17.51±10.09, 17.49±10.16, 17.31±10.08 and 17.28±10.06 respectively.

Table 4.10 Scar's length in the segments was treated with intralesional corticosteroid injections and pulsed dye laser (groups II) in each treatment sessions (n=16).

Duration	Mean (mm)	SD	Min	Max
Baseline	17.21	8.90	6.22	45.56
Wk 4	17.10	8.90	6.53	45.62
Wk 8	17.10	8.99	5.76	45.66
Wk 12	17.03	8.95	5.87	45.61

Table 4.10 Reports Scar's length of groups II in Mean, Standard deviation, Minimum and Maximum value in each sessions of treatment. Scar's length at baseline, weeks 4 8 and 12 were 17.21±8.9, 17.1±8.9, 17.1±8.99 and 17.03±8.95 respectively.

Table 4.11 Comparison the mean scar's length between baseline and each treatment sessions in segments was treated with intralesional corticosteroid injections alone (groups I).

Duration	Mean±SD (mm)	Paired Difference	*p*-value
Baseline – Wk 4	17.51±10.09	0.023±0.25	0.959
	17.49±10.16		
Baseline – Wk 8	17.51±10.09	0.200±0.41	0.083
	17.31±10.08		
Baseline – Wk 12	17.51±10.09	0.230±0.45	0.074
	17.28±10.06		

Note. Mean scar's length between baseline and each treatment sessions was compared using Wilcoxon match pair sign rank test, p value < 0.05 denote significant difference.

Table 4.11 Comparison the mean scar's length between baseline and each treatment sessions in segments was treated with intralesional corticosteroid injections alone.

After the first treatment (Weeks 4): There was no significant difference between mean scar's length at baseline (17.51±10.09) and weeks 4 (17.49±10.16) (p = 0.959). The mean difference between two groups was 0.023. The difference in mean scar's length between baseline and weeks 4 did not reach significance (p = 0.959).

After the second treatment (Weeks 8): There was no significant difference between mean scar's length at baseline (17.51±10.09) and weeks 8 (17.31±10.08) (p = 0.083). The mean difference between two groups was 0.2. The difference in mean scar's length between baseline and weeks 8 did not reach significance (p = 0.083).

After the third treatment (Weeks 12): There was no significant difference between mean scar's length at baseline (17.51±10.09) and weeks 12 (17.28±10.06) (p = 0.074). The mean difference between two groups was 0.23. The difference in mean scar's length between baseline and weeks 12 did not reach significance (p = 0.074).

Table 4.12 Comparison the mean scar's length between baseline and each treatment sessions in segments treated with intralesional corticosteroid injections and pulsed dye laser (groups II) (n=16).

Duration	Mean±SD (mm)	Paired Difference	*p*-value
Baseline – Wk 4	17.21±8.9	0.11±0.22	0.066
	17.1±8.9		
Baseline – Wk 8	17.21±8.9	0.12±0.29	0.105
	17.1±8.99		
Baseline – Wk 12	17.21±8.9	0.18±0.33	0.062
	17.03±8.95		

Note. Mean scar's length between baseline and each treatment session was compared using Wilcoxon match pair sign rank test, p value < 0.05 denote significant difference.

Table 4.12 Comparison the mean scar's length between baseline and each treatment sessions in segments was treated with intralesional corticosteroid injections and pulsed dye laser (groups II).

After the first treatment (Weeks 4): There was no significant difference between mean scar's length at baseline (17.21±8.9) and weeks 4 (17.1±8.9) (p = 0.066). The mean difference between two groups was 0.11. The difference in mean scar's length between baseline and weeks 4 did not reach significance (p = 0.066).

After the second treatment (Weeks 8): There was no significant difference between mean scar's length at baseline (17.21±8.9) and weeks 8 (17.1±8.99) (p = 0.105). The mean difference between two groups was 0.12. The difference in mean scar's length between baseline and weeks 8 did not reach significance (p = 0.105).

After the third treatment (Weeks 12): There was no significant difference between mean scar's length at baseline (17.21±8.9) and weeks 12 (17.03±8.95) (p = 0.062). The mean difference between two groups was 0.18. The difference in mean scar's length between baseline and weeks 12 did not reach significance (p = 0.062).

4.2.3 Scar's width

Scar's width was evaluated by Caliper before treatment and at weeks 4 8 12. Data is shown in table 4.13.

Table 4.13 Scar's width (mm)

Subject	Group I (TAC)				Group II (TAC+PDL)			
	Baseline	**Wk 4**	**Wk 8**	**Wk 12**	**Baseline**	**Wk 4**	**Wk 8**	**Wk 12**
1	7.88	7.78	7.76	7.67	7.21	7.73	7.64	7.55
2	35.42	35.47	35.61	35.82	30.65	30.57	30.64	30.44
3	10.32	10.23	10.21	10.17	10.78	10.77	10.67	10.54
4	5.76	5.84	5.88	5.82	5.89	5.85	5.79	5.78
5	4.34	4.57	4.48	4.47	4.77	4.75	4.73	4.71
6	6.77	6.74	6.68	6.61	6.75	6.66	6.62	6.54
7	10.34	10.33	10.32	10.18	9.45	9.77	9.68	9.66
8	30.44	30.42	30.41	30.38	30.45	30.44	30.51	30.43
9	30.54	30.44	30.43	30.42	25.45	25.45	25.42	25.41
10	16.56	16.87	16.76	16.65	15.45	15.79	15.74	15.64
11	16.56	16.54	16.55	16.51	15.98	15.86	15.85	15.82
12	19.54	19.53	19.53	19.52	18.86	18.85	18.79	18.76
13	14.67	14.76	14.75	14.68	15.76	15.72	15.46	15.29
14	5.65	5.64	5.61	5.61	6.86	6.97	6.93	6.89
15	10.57	10.32	10.27	10.02	8.46	8.33	8.31	8.27
16	9.47	9.44	9.32	9.18	9.65	9.58	9.41	9.39

Table 4.14 Scar's width in the segments was treated with intralesional corticosteroid injections alone (groups I) in each treatment session (n=16).

Duration	Mean	SD	Min	Max
Baseline	14.68	9.97	4.34	35.42
Wk 4	14.68	9.96	4.57	35.47
Wk 8	14.66	9.78	4.48	35.61
Wk 12	14.61	9.81	4.47	35.82

Table 4.14 Reports scar's width of groups I in Mean, Standard deviation, Minimum and Maximum value in each sessions of treatment. Scar's width at baseline, weeks 4 8 and 12 were 14.68±9.97, 14.68±9.96, 14.66±9.78 and 14.61±9.81 respectively.

Table 4.15 Scar's width in the segments was treated with intralesional corticosteroid injections and pulsed dye laser (groups II) in each treatment sessions (n=16).

Duration	Mean (mm)	SD	Min	Max
Baseline	13.90	8.54	4.77	30.65
Wk 4	13.94	8.50	4.75	30.57
Wk 8	13.89	8.53	4.73	30.64
Wk 12	13.82	8.51	4.71	30.44

Table 4.15 Reports Scar's width of groups II in Mean, Standard deviation, Minimum and Maximum value in each sessions of treatment. Scar's width at baseline, weeks 4 8 and 12 were 13.9±8.54, 13.94±8.5, 13.89±8.53 and 13.82±8.51 respectively.

Table 4.16 Comparison the mean scar's width between baseline and each treatment sessions in segments was treated with intralesional corticosteroid injections alone (groups I) (n=16).

Duration	Mean±SD (mm)	Paired Difference	*p*-value
Baseline – Wk 4	14.68±9.97	-0.060±0.13	0.587
	14.68±9.96		
Baseline – Wk 8	14.68±9.97	0.016±0.14	0.587
	14.66±9.78		
Baseline – Wk 12	14.68±9.97	0.070±0.21	0.115
	14.61±9.81		

Note. Mean scar's width between baseline and each treatment sessions was compared using Wilcoxon match pair sign rank test, p value < 0.05 denote significant difference.

Table 4.16 Comparison the mean scar's width between baseline and each treatment sessions in segments was treated with intralesional corticosteroid injections alone.

After the first treatment (Weeks 4): There was no significant difference between mean scar's width at baseline (14.68±9.97) and weeks 4 (14.68±9.96) (p = 0.587). The mean difference between two groups was 0.06. The difference in mean scar's width between baseline and weeks 4 did not reach significance (p = 0.587).

After the second treatment (Weeks 8): There was no significant difference between mean scar's width at baseline (14.68±9.97) and weeks 8 (14.66±9.78) (p = 0.587). The mean difference between two groups was 0.016. The difference in mean scar's width between baseline and weeks 8 did not reach significance (p = 0.587).

After the third treatment (Weeks 12): There was no significant difference between mean scar's width at baseline (14.68±9.97) and weeks 12 (14.61±9.81) (p = 0.115). The mean difference between two groups was 0.07. The difference in mean scar's width between baseline and weeks 12 did not reach significance (p = 0.115).

Table 4.17 Comparison the mean scar's width between baseline and each treatment sessions in segments was treated with intralesional corticosteroid injections and pulsed dye laser (groups II) (n=16).

Duration	Mean±SD (mm)	Paired Difference	*p*-value
Baseline – Wk 4	13.90±8.54	-0.42±0.19	0.649
	13.94±8.5		
Baseline – Wk 8	13.90±8.54	0.01±0.19	0.393
	13.89±8.53		
Baseline – Wk 12	13.90±8.54	0.08±0.20	0.103
	13.82±8.51		

Note. Mean scar's width between baseline and each treatment session was compared using Wilcoxon match pair sign rank test, p value < 0.05 denote significant difference.

Table 4.17 Comparison the mean scar's width between baseline and each treatment sessions in segments was treated with intralesional corticosteroid injections and pulsed dye laser (groups II).

After the first treatment (Weeks 4): There was no significant difference between mean scar's width at baseline (13.9±8.54) and weeks 4 (13.94±8.5) (p = 0.649). The mean difference between two groups was 0.42. The difference in mean scar's width between baseline and weeks 4 did not reach significance (p = 0.649).

After the second treatment (Weeks 8): There was no significant difference between mean scar's width at baseline (13.9±8.54) and weeks 8 (13.89±8.53) (p = 0.393). The mean difference between two groups was 0.01. The difference in mean scar's width between baseline and weeks 8 did not reach significance (p = 0.393).

After the third treatment (Weeks 12): There was no significant difference between mean scar's width at baseline (13.9±8.54) and weeks 12 (13.82±8.51) (p = 0.103). The mean difference between two groups was 0.08. The difference in mean scar's width between baseline and weeks 12 did not reach significance (p = 0.103).

4.2.4 Scar's Pliability

Scar's pliability was evaluated by cutometer before treatment and at weeks 4 8 12. Data is shown in table 4.18.

Table 4.18 Scar's pliability

Subject	Group I (TAC)				Group II (TAC+PDL)			
	Baseline	**Wk 4**	**Wk 8**	**Wk 12**	**Baseline**	**Wk 4**	**Wk 8**	**Wk 12**
1	0.45	0.48	0.49	0.51	0.41	0.43	0.65	0.81
2	0.53	0.58	0.61	0.73	0.51	0.42	0.52	0.87
3	0.61	0.60	0.77	0.82	0.53	0.51	0.63	0.88
4	0.47	0.51	0.50	0.83	0.39	0.48	0.64	0.85
5	0.44	0.49	0.65	0.91	0.45	0.44	0.77	0.89
6	0.62	0.68	0.72	0.87	0.68	0.64	0.85	0.96
7	0.33	0.36	0.41	0.78	0.37	0.39	0.48	0.62
8	0.21	0.20	0.28	0.76	0.29	0.34	0.51	0.71
9	0.27	0.25	0.31	0.66	0.32	0.41	0.40	0.63
10	0.58	0.51	0.62	0.82	0.50	0.55	0.76	0.70
11	0.42	0.49	0.51	0.65	0.57	0.50	0.74	0.72
12	0.28	0.29	0.32	0.79	0.24	0.33	0.78	0.91
13	0.63	0.65	0.64	0.88	0.55	0.56	0.71	0.78
14	0.71	0.70	0.63	0.79	0.77	0.81	0.86	0.97
15	0.64	0.61	0.60	0.92	0.66	0.69	0.80	0.93
16	0.65	0.66	0.52	0.71	0.75	0.77	0.95	0.98

Table 4.19 Scar's pliability in the segments was treated with intralesional corticosteroid injections alone (groups I) in each treatment sessions (n=16).

Duration	Mean	SD	Min	Max
Baseline	0.49	0.16	0.21	0.71
Wk 4	0.50	0.16	0.20	0.70
Wk 8	0.54	0.15	0.28	0.77
Wk 12	0.68	0.11	0.51	0.92

Table 4.19 Reports Scar's pliability of groups I in Mean, Standard deviation, Minimum and Maximum value in each sessions of treatment. Scar's pliability at baseline, weeks 4 8 and 12 were 0.49±0.16, 0.5±0.16, 0.54±0.15 and 0.68±0.11 respectively. Mean scar's pliability was increased in every treatment sessions.

Table 4.20 Scar's pliability in the segments was treated with intralesional corticosteroid injections and pulsed dye laser (groups II) in each treatment sessions (n=16).

Duration	Mean	SD	Min	Max
Baseline	0.50	0.16	0.24	0.77
Wk 4	0.52	0.15	0.33	0.81
Wk 8	0.69	0.15	0.40	0.95
Wk 12	0.83	0.12	0.62	0.98

Table 4.20 Reports scar's pliability of groups II in Mean, Standard deviation, Minimum and Maximum value in each sessions of treatment. Scar's pliability at baseline, weeks 4 8 and 12 were 0.5±0.16, 0.52±0.15, 0.69±0.15 and 0.83±0.12 respectively. Mean scar's pliability was increased in every treatment sessions.

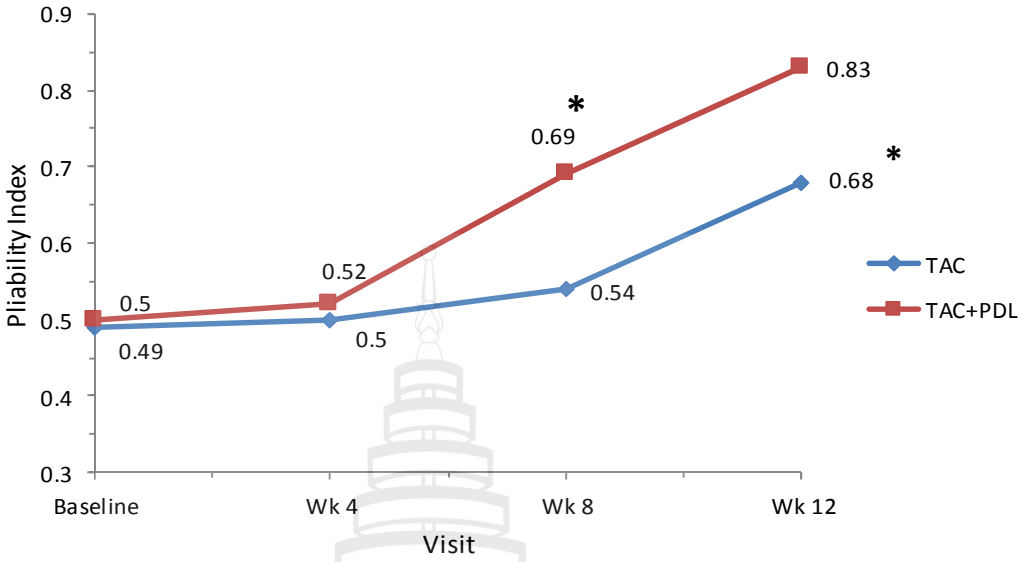


Figure 4.2 Mean scar's pliability of both groups in each treatment sessions

Figure 4.2 Presents the mean scar's pliability in both groups on each treatment sessions. Mean scar's pliability in both groups was increased in every treatment sessions. After 2 treatment mean scar's pliability in TAC+PDL groups was decreased significantly (p<0.001) when compare with baseline (*). After 3 treatment mean scar's pliability in TAC groups was decreased significantly (p<0.001) when compare with baseline (*).

Table 4.21 Comparison the mean scar's pliability between baseline and each treatment sessions in segments was treated with intralesional corticosteroid injections alone (groups I) (n=16).

Duration	Mean±SD	Paired Difference	*p*-value
Baseline – Wk 4	0.49±0.16	-0.01±0.04	0.162
	0.50±0.16		
Baseline – Wk 8	0.49±0.16	-0.05±0.08	0.052
	0.54±0.15		
Baseline – Wk 12	0.49±0.16	-0.19±0.16	<0.001
	0.68±0.11		

Note. Mean scar's pliability between baseline and each treatment sessions was compared using paired t-test, p value < 0.05 denote significant difference.

Table 4.21 Comparison the mean scar's pliability between baseline and each treatment session in segment was treated with intralesional corticosteroid injections alone.

After the first treatment (Weeks 4): There was no significant difference between mean scar's pliability at baseline (0.49 ± 0.16) and weeks 4 (0.5 ± 0.16) (p = 0.162). The mean difference between two groups was 0.01. The difference in mean scar's pliability between baseline and weeks 4 did not reach significance (p = 0.16).

After the second treatment (Weeks 8): There was no significant difference between mean scar's pliability at baseline (0.49 ± 0.16) and weeks 8 (0.54 ± 0.15) (p = 0.052). The mean difference between two groups was 0.05. The difference in mean scar's pliability between baseline and weeks 8 did not reach significance (p = 0.052).

After the third treatment (Weeks 12): The mean scar's pliability at weeks 12 (0.68 ± 0.11) was significantly higher than baseline (0.49 ± 0.16) (p < 0.001). The mean difference between two groups was 0.19. The scar's pliability at weeks 12 was increased from baseline significantly (p < 0.001).

Table 4.22 Comparison the mean scar's pliability between baseline and each treatment session in segments was treated with intralesional corticosteroid injections and pulsed dye laser (groups II) (n=16).

Duration	Mean±SD	Paired Difference	*p*-value
Baseline – Wk 4	0.50±0.16	-0.02±0.05	0.212
	0.52±0.15		
Baseline – Wk 8	0.50±0.16	-0.19±0.12	<0.001
	0.69±0.15		
Baseline – Wk 12	0.50±0.16	-0.33±0.13	<0.001
	0.83±0.12		

Note. Mean scar's pliability between baseline and each treatment session was compared using paired t-test, p value < 0.05 denote significant difference.

Table 4.22 Comparison the mean scar's pliability between baseline and each treatment sessions in segments was treated with intralesional corticosteroid injections and pulsed dye laser.

After the first treatment (Weeks 4): There was no significant difference between mean scar's pliability at baseline (0.5 ± 0.16) and weeks 4 (0.52 ± 0.15) ($p = 0.212$). The mean difference between two groups was 0.02. The difference in mean scar's pliability between baseline and weeks 4 did not reach significance ($p = 0.212$).

After the second treatment (Weeks 8): The mean scar's pliability at weeks 8 (0.69 ± 0.15) was significantly higher than baseline (0.5 ± 0.16) ($p < 0.001$). The mean difference between two groups was 0.19. The scar's pliability at weeks 8 was increased form baseline significantly ($p < 0.001$).

After the third treatment (Weeks 12): The mean scar's pliability at weeks 12 (0.83 ± 0.12) was significantly higher than baseline (0.5 ± 0.16) ($p < 0.001$). The mean difference between two groups was 0.33. The scar's pliability at weeks 12 was increased form baseline significantly ($p < 0.001$).

Table 4.23 Comparison the difference of mean scar's pliability in each treatment sessions between groups I and groups II.

Difference of Mean Pliability	Group I (TAC)	Group II (TAC + PDL)	Paired Differences	*p*-value
Baseline – Wk 4	-0.01±0.37	-0.02±0.05	0.004±0.02	0.855
Baseline – Wk 8	-0.05±0.08	-0.19±0.12	0.150±0.14	0.010
Baseline – Wk 12	-0.19±0.16	-0.33±0.13	0.140±0.14	0.045

Note. The difference of mean scar's pliability in each treatment sessions between groups I and groups II was compared using paired t-test, p value < 0.05 denote significant difference.

Table 4.23 Comparison the difference of mean scar's pliability in each treatment sessions between groups I and groups II.

After the first treatment (Weeks 4): There was no significant difference between the improvement of mean scar's pliability in groups I (0.01 ± 0.37) and groups II (0.02 ± 0.05) (p = 0.855). The mean difference between two groups was 0.004. The improvement of mean scar's pliability between groups I and groups II at weeks 4 did not reach significance (p = 0.855).

After the second treatment (Weeks 8): The improvement of mean scar's pliability in groups I (0.05 ± 0.08) was significantly higher than groups II (0.19 ± 0.12) (p=0.01). The improvement of mean scar's pliability between two groups was 0.15. At weeks 8 the improvement of mean scar's pliability in groups II was better than groups I significantly (p = 0.01).

After the third treatment (Weeks 12): There was no significant difference between the improvement of mean scar's pliability in groups I (0.19 ± 0.16) and groups II (0.33 ± 0.13) (p = 0.045). The mean difference between two groups was 0.14. The improvement of mean scar's pliability between groups I and groups II at weeks 12 reach significance (p = 0.045).

4.2.4 Scar's Erythema

Scar's erythema was evaluated by mexameter before treatment and at weeks 4 8 12. Data is shown in table 4.23.

Table 4.24 Scar's Erythema

Subject	Group I (TAC)				Group II (TAC+PDL)			
	Baseline	**Wk 4**	**Wk 8**	**Wk 12**	**Baseline**	**Wk 4**	**Wk 8**	**Wk 12**
1	310.33	329.00	311.67	333.00	297.00	299.67	359.00	320.67
2	333.00	328.33	340.00	317.67	342.00	319.00	327.00	401.00
3	276.67	246.00	256.67	295.00	360.00	343.67	332.67	345.67
4	366.00	362.33	360.00	357.00	366.00	349.00	331.33	316.67
5	339.00	319.67	303.00	302.67	370.50	358.33	345.00	375.00
6	280.00	360.00	296.67	380.00	300.60	259.60	286.00	214.67
7	383.30	231.00	251.33	275.00	449.30	438.33	417.67	408.67
8	279.30	409.00	410.00	444.67	247.00	216.00	206.33	375.00
9	440.00	529.67	487.00	535.00	500.33	566.33	553.00	507.00
10	484.67	563.67	463.00	553.00	401.00	398.67	388.00	396.00
11	401.00	484.67	396.00	501.67	408.00	382.33	377.67	363.33
12	455.00	485.33	577.67	562.33	510.33	507.67	485.00	463.00
13	509.00	523.33	554.00	519.00	502.00	498.00	509.67	538.00
14	467.33	506.00	551.00	566.67	477.00	470.00	545.00	575.00
15	590.67	514.00	528.67	501.00	562.00	420.00	408.33	391.67
16	371.33	508.33	427.00	450.00	496.00	571.33	550.00	548.00

Table 4.25 Mean scar's erythema in the segments was treated with intralesional corticosteroid injections alone (groups I) in each treatment sessions.

Duration	Mean	SD	Min	Max
Baseline	392.91	91.81	276.67	590.67
Wk 4	418.77	108.20	231.00	563.67
Wk 8	407.11	110.14	251.33	579.00
Wk 12	430.86	106.26	275.00	566.67

Table 4.25 Reports Scar's erythema of groups I in Mean, Standard deviation, Minimum and Maximum value in each sessions of treatment. Mean scar's erythema at baseline, weeks 4 8 and 12 were 392.91±91.81, 418.77±108.2, 407.11±110.14 and 430.86±106.26 respectively.

Table 4.26 Mean scar's erythema in the segments was treated with intralesional corticosteroid injections and pulsed dye laser (groups II) in each treatment sessions.

Duration	Mean	SD	Min	Max
Baseline	411.82	91.35	247.00	562
Wk 4	399.87	104.24	216.00	571
Wk 8	401.35	102.30	206.33	550
Wk 12	408.71	96.29	189.33	575

Table 4.26 Reports Scar's erythema of groups II in Mean, Standard deviation, Minimum and Maximum value in each sessions of treatment. Scar's erythema at baseline, weeks 4 8 and 12 were 411.82±91.35, 399.87±104.24, 401.35±102.3 and 408.71±96.29 respectively.

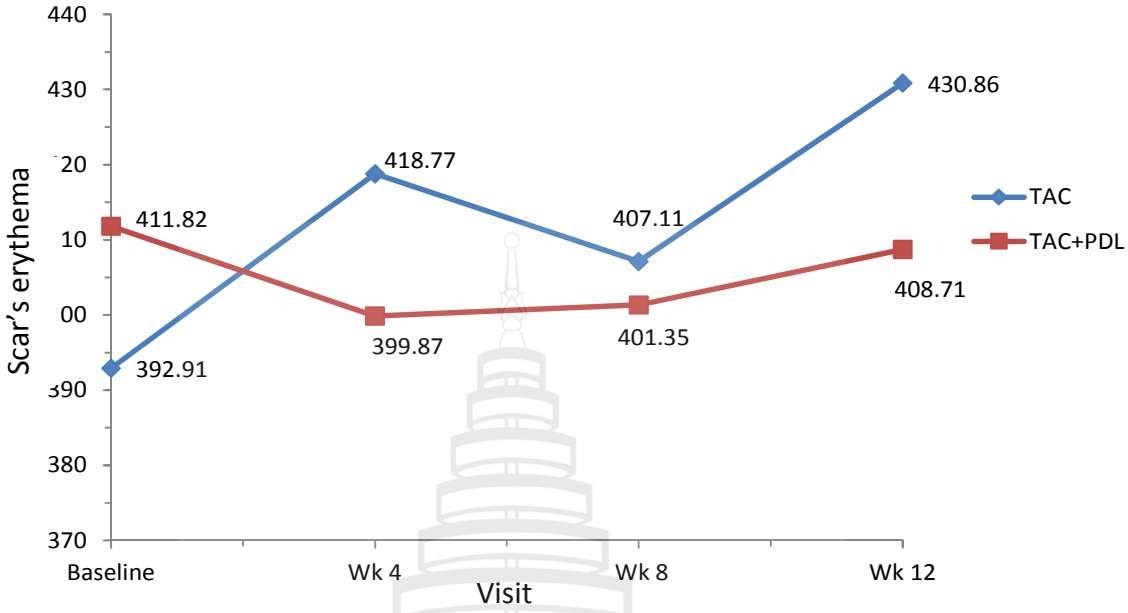


Figure 4.3 Mean scar's erythema of both groups in each treatment sessions

Figure 4.3 Presents the mean scar's erythema in both groups on each treatment sessions. The erythema of the scar, as evaluated by mexameter MX18 showed no significant difference in comparison of erythema at baseline and at every follow-up visit.

Table 4.27 Comparison the mean scar's erythema between baseline and each treatment sessions in segments was treated with intralesional corticosteroid injections alone (groups I).

Duration	Mean±SD	Paired Difference	*p*-value
Baseline – Wk 4	392.91±91.81 418.77±108.2	-25.86±75.7	0.192
Baseline – Wk 8	392.91±91.81 407.11±110.14	-14.19±66.86	0.409
Baseline – Wk 12	392.91±91.81 430.86±106.26	-37.94±76.63	0.066

Note. Mean scar's erythema between baseline and each treatment session were compared using paired t-test, p value < 0.05 denote significant difference.

Table 4.27 Comparison the mean scar's erythema between baseline and each treatment session in segment was treated with intralesional corticosteroid injections alone.

After the first treatment (Weeks 4): There was no significant difference between mean scar's erythema at baseline (392.91±91.81) and weeks 4 (418.77±108.2) (p = 0.192). The mean difference between two groups was 25.86. The difference in mean scar's erythema between baseline and weeks 4 did not reach significance (p = 0.192).

After the second treatment (Weeks 8): There was no significant difference between mean scar's erythema at baseline (392.91±91.81) and weeks 8 (407.11±110.14) (p = 0.409). The mean difference between two groups was 14.19. The difference in mean scar's erythema between baseline and weeks 8 did not reach significance (p = 0.409).

After the third treatment (Weeks 12): There was no significant difference between mean scar's erythema at baseline (392.91±91.81) and weeks 12 (430.86±106.26) (p = 0.066). The mean difference between two groups was 37.94. The difference in mean scar's erythema between baseline and weeks 12 did not reach significance (p = 0.066).

Table 4.28 Comparison the mean scar's erythema between baseline and each treatment sessions in segments treated with intralesional corticosteroid injections and pulsed dye laser (groups II).

Duration	Mean±SD	Paired Difference	*p*-value
Baseline – Wk 4	411.82±91.35	11.95±46.65	0.322
	399.87±104.24		
Baseline – Wk 8	411.82±91.35	10.46±53.85	0.449
	401.35±106.79		
Baseline – Wk 12	411.82±91.35	3.11±72.52	0.866
	408.71±115.76		

Note. Mean scar's erythema between baseline and each treatment session were compared using paired t-test, p value < 0.05 denote significant difference.

Table 4.28 Comparison the mean scar's erythema between baseline and each treatment sessions in segment treated with intralesional corticosteroid injections and pulsed dye laser (groups II).

After the first treatment (Weeks 4): There was no significant difference between mean scar's erythema at baseline (411.82±91.35) and weeks 4 (399.87±104.24) (p = 0.322). The mean difference between two groups was 11.95. The difference in mean scar's erythema between baseline and weeks 4 did not reach significance (p = 0.322).

After the second treatment (Weeks 8): There was no significant difference between mean scar's erythema at baseline (411.82±91.35) and weeks 8 (401.35±106.79) (p = 0.449). The mean difference between two groups was 10.46. The difference in mean scar's erythema between baseline and weeks 8 did not reach significance (p = 0.449).

After the third treatment (Weeks 12): There was no significant difference between mean scar's erythema at baseline (411.82±91.35) and weeks 12 (408.71±115.76) (p = 0.866). The mean difference between two groups was 3.11. The

difference in mean scar's erythema between baseline and weeks 12 did not reach significance (p = 0.866).

Table 4.29 Comparison the difference of mean scar's erythema in each treatment sessions between groups I and groups II.

Difference of Mean erythema	Group I (TAC)	Group II (TAC + PDL)	Paired Differences	*p*-value
Baseline – Wk 4	-25.86±75.70	11.95±46.65	-37.80±67.98	0.052
Baseline – Wk 8	-14.19±66.86	10.46±53.85	-24.65±67.59	0.165
Baseline – Wk 12	-37.94±76.63	3.11±72.52	-41.05±77.28	0.051

Note. The difference of mean scar's erythema in each treatment sessions between groups I and groups II were compared using paired t-test, p value < 0.05 denote significant difference.

Table 4.29 Comparison the difference of mean scar's erythema in each treatment sessions between groups I and groups II.

After the first treatment (Weeks 4): There was no significant difference between the improvement of mean scar's erythema in groups I (-25.86±75.7) and groups II (11.95±46.65) (p = 0.052). The mean difference between two groups was 37.8. The improvement of mean scar's erythema between groups I and groups II at weeks 4 did not reach significance (p = 0.052).

After the second treatment (Weeks 8): There was no significant difference between the improvement of mean scar's erythema in groups I (-14.19±66.86) and groups II (10.46±53.85) (p = 0.165). The mean difference between two groups was 24.65. The improvement of mean scar's erythema between groups I and groups II at weeks 8 did not reach significance (p = 0.165).

After the third treatment (Weeks 12): There was no significant difference between the improvement of mean scar's erythema in groups I (-37.94±76.63) and groups II (3.11±72.52) (p = 0.051). The mean difference between two groups was 41.05. The improvement of mean scar's erythema between groups I and groups II at weeks 12 did not reach significance (p = 0.051).

4.3 The Satisfaction and Side Effects

Patient satisfaction rating was subjectively measured at last follow-up visits (weeks 12) on a visual analog scale (VAS) ranging from 0 to 4.

0 = no improvement

1= <25% (mild) improvement

2= 25-50% (moderate) improvement

3= 51-75% (good) improvement

4= >75% (excellent) improvement.

Table 4.30 Patient's satisfaction

Satisfaction grade	Groups I (TAC) N(%)	Groups II TAC+PDL) N(%)
no improvement	0	0
mild improvement	0	0
moderate improvement	5 (31.25%)	3 (18.75%)
good improvement	10 (62.5%)	10 (62.5%)
excellent improvement	1 (6.25%)	3 (18.75%)

After being treated with intralesional corticosteroid injections, most of the patients rated good improvement of their scar 10 peoples (62.5%), Moderate improvement 5 peoples (31.25%) and Excellent improvement 1 people (6.25%). After being treated with intralesional corticosteroid injections and pulsed dye laser , most of

the patients rated Good improvement 10 peoples (62.5%), moderate improvement 3 peoples (18.75%), and Excellent improvement 3 people (18.75%).

Table 4.31 Comparison the patient's satisfaction of treatment.

	Mean ±SD	***p*-value**
Groups I (TAC)	2.75±0.58	
Groups II (TAC+PDL)	3.00±0.63	
Difference of satisfaction grade	0.25±0.77	p=0.206

Table 4.31 presents the mean patient's satisfaction of treatment. The segments was treated with intralesional corticosteroid injections mean patient's satisfaction was 2.74±0.58, and The segment treated with intralesional corticosteroid injections and pulsed dye laser mean patient's satisfaction was 3±0.63. There was no statistical significance in the mean difference of patient's satisfaction grade between two groups (p = 0.206).

Table 4.32 Side effect of treatment evaluated by dermatologist

Side effect	**Groups I (TAC)**	**Groups II (TAC+PDL)**
After first treatment		
Telangiectasia	-	-
Skin atrophy	-	-
Hyperpigmentation	-	-
Hypopigmentation	-	-
Purpura	-	2(12.5%)
Crusting	-	-
Burn	-	-
Other	-	-

Table 4.32 (Continue)

Side effect	Groups I (TAC)	Groups II (TAC+PDL)
After second treatment		
Telangiectasia	3(18.75%)	3(18.75%)
Skin atrophy	-	-
Hyperpigmentation	-	-
Hypopigmentation	-	-
Purpura	-	3(18.75%)
Crusting	-	-
Burn	-	-
Other	-	-
After third treatment		
Telangiectasia	3(18.75%)	3(18.75%)
Skin atrophy	-	-
Hyperpigmentation	2(12.5%)	2(12.5%)
Hypopigmentation	-	-
Purpura	-	3(18.75%)
Crusting	-	-
Burn	-	-
Other	-	-

The study did not show any serious side effects. After first treatment, there were 2 (12.5%) subjects had purpura and mild edema which were the disappeared within 1 week.

After second treatment, there were 3 (18.75%) subjects had telangiectasia in both groups and 3(18.75%) subjects had purpura and mild edema which were the disappeared within 1 week.

After third treatment, there were 3 (18.75%) subjects had telangiectasia in both groups, 2 (12.5%) subjects had hyperpigmentation and 3 (18.75%) subjects had purpura and mild edema which were the disappeared within 1 week. No other adverse effects such as crusting burn were demonstrated.

CHAPTER 5

DISCUSSION AND CONCLUSION

5.1 Discussion

Although the basis of keloid and hypertrophic scar formation has not been clearly understood, an imbalance between matrix degradation and collagen biosynthesis resulting into excess collagen accumulation in the wound has been postulated. Normally, fibroblasts construct new extracellular matrix, initiate collagen synthesis, and provide wound edge tension along contractile proteins; actin and desmin. On the other hand, hypertrophic scar-derived fibroblasts produce increased amount of collagen per cell compared with normal fibroblasts (Manuskiatti & Fitzpatrick, 2002). Accordingly, the suppression of overwhelming and uncontrolled fibroblast activity in keloid and hypertrophic scars may be an essential approach during treatment of this abnormal wound healing. However, keloid and hypertrophic scar formation remains a difficult problem to eradicate. This is not only due to the high recurrence rate; where 46.15% of the scars in the present study were recurrent, but due to the incidence of side effects associated with treatment as well (Alster, 2002).

The effectiveness of pulse dye laser treatment of keloid and hypertrophic scars is hypothesized to be mediated to the selective photothermolytic effect of pulse dye laser on scars' microvasculature with consequent wound ischemia. Moreover, the improvement in skin texture of scars treated with pulse dye laser was found to be an interesting observation that adds a significant favorable outcome. This textural improvement is suggested to be due to collagen remodeling, the same concept for the improvement seen with pulse dye laser treatment of photoaged skin (Elwakil, 2009).

Previous study, Wittenberg et al., reported that there was no clinical improvement with 4 pulse dye laser (585nm) sessions. In contrast, Goldman and Fitzpatrick reported the reverse. This positive result is confirmed in the present study, where flattening of the scars at both groups was observed about as early as the 16th week after pulse dye laser treatment (4 weeks after the 4th treatment session). Moreover, higher rate of scar flattening was elicited after more than two pulse dye laser treatment sessions. Accordingly, multiple and sequential pulse dye laser treatment sessions are essential to achieve better clinical outcome.

All intralesional formulas have shown comparable results in keloid and hypertrophic scar flattening. They have been suggested to have higher effectiveness than laser treatment. The role of intralesional corticosteroid injections for treatment of keloid and hypertrophic scars has been well-established. The suppression mechanisms of intralesional corticosteroid injection on wound healing include; first, the interruption of the inflammatory cell migration and phagocytosis. Second, it induces vasoconstriction resulting into deprivation of oxygen and nutrients in the wound. Third, it has an anti-mitotic activity on fibroblasts and keratinocytes (Manuskiatti & Fitzpatrick, 2002). Collectively, intralesional corticosteroid injection was reported to produce objective improvements in hypertrophic scar volume and symptoms especially for those scars of more than 6 months' duration.

Triamcinolone acetonamide (TAC) is the most commonly used corticosteroid for treatment of keloid and hypertrophic scars. Although intralesional TAC injection has shown clinical efficacy, the results have been uncertain and frequently associated with many side effects including; pigmentary changes, and dermal atrophy (Asilian, Darougheh & Shariati, 2006).

Theoretically, the combination therapy is supposed to be of value in order to achieve better results and to minimize the associated complications. However, there is a debate about the effectiveness of the combined treatment of pulse dye laser and intralesional TAC injections. Recently, others reported the effectiveness of this combination (Karrrer, Bosserhoff & Weiderer, 2003).

5.1.1 Demography

5.1.1.1 Sex: In general, keloids and hypertrophic scars can affect both males and females equaly (Alster & Tanzi, 2003) but in our study there were relatively have more male subjects than females, probably because male individuals are more frequently subjected to trauma than females.

5.1.1.2 Age: In our study, the mean age of patients with keloids and hypertrophic scars was 25.06 ± 6.98 years that was similar to the study of Harting et al. (Harting et al., 2008) reported that keloid and hypertrophic scars has age peaks at 20-29 years.

5.1.1.3 Skin photo type: Keloids are 15 times as likely to occur in darkerskinned individuals points to genetic influences. Keloid formation mainly occurs in parts of the body with high concentrations of melanocytes, and it is rare on the soles and palms (Wolfram et al., 2009). The same as our study, most of the subjects had Fitzpatrick skin type IV 10 subjects, the others were type III and V 3 subjects.

5.1.1.4 Affected areas: In our study the most commonly affected area were extremities 8 subjects followed by trunk 7 subjects that was similar to the study of Harting et al. (Harting et al., 2008) reported that skin or wound tension has also been implicated as a critical factor in hypertrophic scars and keloids, areas of high tension such as chest back shoulder and joint. And similar to Rudolph, reported that scars that cross joints or skin creases at a right angle are predisposed to form hypertrophic scars because of the constant tension forces that occur (Rudolph, 1987).

5.1.2 Scar's Dimensions

Elwakil and colleagues used TAC+PDL treatment 13 hypertrophic scars. They demonstrated favorable improvements in scar height, pliability, erythema, and scar's symptom with minimal side effects and treatment discomfort. The higher rate of scar flattening was elicited after more than two PDL treatment sessions. Similarly, in our study all keloid and hypertrophic scar showed significant flattening after laser treatments at both TAC (p<0.001), and TAC+PDL (p<0.001) segments. A significant flattening, compared with baseline measurements was noted after two treatments sessions. And after the third treatment (Weeks 12), the reduction of mean scar's

height in combined treatment (TAC+PDL) was higher than TAC treatment but not reach significant (p=0.165). No significant statistical change was observed in scars' length, and width same as Elwakil study **(**Elwakil, 2009).

In comparison with TAC group, it seems that TAC + PDL combination is more effective but there not reach statistical significant. Skin phototype is factor that may influence the therapeutic outcome. Although many studies have examined the roles of PDL for treatment of hypertrophic scars and keloids, most evaluated only light-skinned patients. Kono et al. reported that high melanin in dark-skinned patients is a competitive chromophore to haemoglobin during PDL treatment leading to a decreased treatment response and an increased risk of side effects (Kono et al., 2005). Chan and colleagues report that in dark-skinned individuals, the increase in nonspecific thermal injury owing to epidermal melanin absorption can result in a poorer outcome (Chan et al., 2004). In commonly among Thai people usually have high epidermal melanin. In our study most of the subjects had Fitzpatrick skin type IV 10 subjects and skin type V 3 subjects. So the result may not effective as that obtained in white skinned patients.

The frequency of treatment and number of sessions are the factor that may influence the therapeutic outcome. Wittenberg et al., reported that there was no clinical improvement with 4 PDL (585nm) sessions (Wittenberg et al., 1999). In contrast, Goldman and Fitzpatrick reported the reverse (Goldman & Fitzpatrick, 1995). This positive result is confirmed in our study, where flattening of the scars at both groups was observed about as early as weeks 8 (4 weeks after the 2nd treatment session). Elwakil and colleagues reported that that late treatment of bulky scars (scars duration more than 6 month) needed more frequent PDL sessions (5.15±0.8) compared with the less frequent sessions (4.46±1.13) needed for early treatment of less bulky scars (scars duration less than 6 month). Accordingly, multiple and sequential PDL treatment sessions are essential to achieve better clinical outcome.

5.1.3 Scar's pliability

In our study, scar's pliability of TAC+PDL segments increased significantly over the study period (p<0.001). The improvement of scar elasticity was significant after three TAC treatments (p<0.001) and after two TAC+PDL treatment (p<0.001).

At weeks 8 the improvement of mean scar's pliability in TAC+PDL segments was better than TAC segments significantly (p = 0.01). That was similar to the study of Elwakil, they used TAC+PDL treatment 13 hypertrophic scars and they reported that scar's pliability was increase from baseline significantly (p<0.01) (Elwakil, 2009).

5.1.4 Scar's erythema

Elwakil and colleagues reported that the percentages of erythema clearance after treatment were found to be 62%±12.53% at statistical significances of p<0.01. They used Adobe Photoshop 6.0 ME Software (Adobe System Incorporation, USA) for analyze the erythema of the scars. In our study the erythema of the scar, as evaluated by mexameter MX18 showed no significant difference in comparison at baseline and at every follow-up visit. As pointed out by Chan and associates, skin phototype can affect the mexameter assessment (Chan et al., 2004). This could be due to the measurement being influenced by the content of epidermal melanin, which exists in higher quantities in Asian skin.

5.2 Conclusion

Intralesional corticosteroid injections alone and its combination with pulsed dye laser are effective modalities that could be used for treatment keloid and hypertrophic scars. The adjunctive use of pulsed dye laser did not significantly enhance clinical outcome in our study except in terms of increased scar's elasticity. Different of improvements of scar's height in both groups no statistically significant (p=0.165), the scars' pliability after 2 treatment in TAC+PDL groups were higher than TAC groups significantly (p=0.01). No significant statistical change was observed in scars' length, width and erythema after treatment in both groups. Hyperpigmentation and telangiectasia are still encountered complications.

5.3 Suggestion

5.3.1 Further studies are necessary to determine the long term clinical efficacy and side effect of the combination of pulsed dye laser and intralesional corticosteroid injections.

5.3.2 Further studies will include larger sample size and representative subjects with various skin phototypes.

5.3.3 Additional studies are needed to assess the appropriate number of treatment sessions and interval in order to obtain better clinical outcome.

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APPENDIX

APPENDIX A

PATIENT RECORD FORM

แบบบันทึกข้อมูลโครงการวิจัย

เรื่อง : การศึกษาเปรียบเทียบประสิทธิภาพของการใช้พัลส์ดายเลเซอร์ ร่วมกับยาฉีดสเตียรอยด์เข้ารอยโรค เทียบกับ ยาฉีดสเตียรอยด์อย่างเดียว ในการรักษาแผลเป็นนูนและแผลเป็นคีลอยด์

1. ข้อมูลทั่วไป

ชื่อ……นามสกุล……อายุ…….ปี

ที่อยู่……

……

อาชีพ**.....** เบอร์โทรศัพท์…….....

E-mail : ……

2. ข้อมูลเกี่ยวกับแผลเป็นนูน หรือคีลอยด์

- อายุเมื่อเริ่มเป็น …….. ปี
- ตำแหน่งที่เป็น **.....**
- โรคประจำตัว **.**…….
- มีประวัติคนในครอบครัวเป็นโรคนี้หรือไม่ …….

3. ข้อมูลการรักษาแผลเป็นนูน หรือคีลอยด์

☐ ไม่เคยรักษา ☐ เคยรักษาด้วยยา ☐ เคยรักษาด้วยเลเซอร์

☐ เคยรักษาทั้งสองอย่าง ☐ อื่นๆ

- เคยเกิดผลข้างเคียงจากการรักษา หรือไม่ ……

- ประวัติแพ้ยา ……**....**

4. ข้อมูลการวิจัย

- ชุดการรักษา **.....**

- ประเภทสีผิว (Skin type) I II III IV V VI

- พารามิเตอร์เครื่อง spot size ……. fluence …….Cryogen spray……

APPENDIX B

DOCTOR RECORD FORM

Data record

Patient name.....

Scar's dimensions (height length width)

	TAC				TAC+PDL			
	Wk 0	Wk 4	Wk 8	Wk 12	Wk 0	Wk 4	Wk 8	Wk 12
Height(mm)								
Length(mm)								
Width(mm)								

Scar's pliability

	TAC				TAC+PDL			
	Wk 0	Wk 4	Wk 8	Wk 12	Wk 0	Wk 4	Wk 8	Wk 12
Pliability								

Scar's erythema

	TAC				TAC+PDL			
	Wk 0	Wk 4	Wk 8	Wk 12	Wk 0	Wk 4	Wk 8	Wk 12
Erythema								

Side effect

	TAC				TAC+PDL			
	Wk 0	Wk 4	Wk 8	Wk 12	Wk 0	Wk 4	Wk 8	Wk 12
Hypopigmentation								
Hyperpigmentation								
Telangiectasia								
Epidermal atrophy								

Clinical improvement evaluated by patient

0 = no improvement

1= <25% (mild) improvement

2= 25-50% (moderate) improvement

3= 51-75% (good) improvement

4= >75% (excellent) improvement

Treatment	Score of improvement	Total
TAC		
TAC+PDL		

CURRICULUM VITAE

CURRICULUM VITAE

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