EFFICACY OF 585-595 nm PULSED DYE LASER, 1064 nm ND: YAG LASER AND 10600 nm FRACTIONAL CO_2 LASER FOR KELOID TREATMENT: A SYSTEMATIC REVIEW

BY

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Abstract

Pathological scarring, or keloids, are painful, itchy lesions that develop from abnormal wound healing. It affects the patient's quality of life in both physical and psychological ways. Since the cause of keloids is still unclear, there are no established therapeutic guidelines. The initial line of treatment is a traditional intralesional steroid injection, yet its application is constrained by adverse effects. These days, as laser technology advances, keloids can be effectively treated with various lasers in addition to traditional treatment. The effectiveness of three laser devices—a 585-595 nm pulsed dye laser, a 1064 nm Nd: YAG laser, and a 10600 nm fractional carbon dioxide laser—in treating keloids is examined in this systematic review. We looked through SCOPUS, Cochrane Controlled Trials Register, and PubMed for relevant articles published between 1st January 2010 to 6th September 2023. Research details, data on scar characteristics, and result evaluations on validated scar measures were among the extracted data.

There was heterogeneity in a lot of aspects: types of lasers used and laser parameters, treatment duration, scar size and age, skin type, etiology of scars, scar assessment scales, and treatment follow-up. In comparison to laser alone and other conventional procedures, the combination of laser plus intralesional steroids or verapamil produces a higher improvement in scar features and increases patient satisfaction. When using a fractional carbon dioxide laser, pliability is the most noticeable scar feature and PDL improved scar vascularity at a somewhat higher rate than other laser types. To validate these findings, more research in the form of randomized trials using similar standardized scar measures is required.

(Total 133 pages)

Keywords: keloid scar, carbon dioxide laser, pulsed dye laser, Nd: YAG laser

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Abbreviations and Symbols

Symbol	Meaning
5-FU	5-fluorouracil
ACE	angiotensin-converting enzyme
CDU	color doppler ultrasound
CO_2	carbon dioxide
CTGF	connective tissue growth factor
DNA	deoxyribonucleic acid
ECM	extracellular matrix
Er: YAG	erbium-doped yttrium aluminium garnet
FCL	fractional carbon dioxide
HTS	hypertrophic scar
Ig E	immunoglobulin E
IL - 6	Interleukin - 6
IL corticosteroid	Intralesional corticosteroid
LP – Nd : YAG	long pulsed neodynium yttrium aluminium garnet
LSCI	laser speckle contrast imaging
mRNA	messenger ribonulceic acid
mVSS	modified vancouver scar scale
MMP	matrix metalloproteinase
MQS	manchester quartile score
MTZs	microthermal treatment zones
Nd : YAG	neodynium yttrium aluminium garnet
NF-κB	nuclear kappa light chain enhancer of activated B cells
NOS	newcastle-ottawa scale
OCEBM	oxford centre for evidence-based medicine
p53	transformation related protein 53
PDGF	platelet-derived growth factor
PDL	pulsed dye laser
PGE2	prostaglandin E2

Abbreviations and Symbols (cont.)

Symbol	Meaning
POSAS	patient and observer scar assessment scale
QS – Nd: YAG	quality switch neodynium yttrium aluminium garnet
RCT	randomized controlled trial
RNA	ribonucleic acid
TAC	triamcinolone acetonide
TCA	trichloroacetic acid
TGF - β	transforming growth factor - beta
TIMPs	tissue inhibitors of metalloproteinases
UFCL	ultrapulse fractional carbon dioxide laser
VAS	visual analog scale
VEGF	vascular endothelial growth factor
VSS	vancouver scar scale

Chapter 1

Introduction

1.1 Background and Significance of the Problem

When our body is insulted by injury or by some invasive procedures, there is a break in the skin integrity and a wound appears. The normal wound healing process undergoes four stages: Hemostasis, Inflammation, Proliferation, and Remodeling. When these stages go against the normal course, pathological scars have emerged. Keloids are one of those scars that appear due to fibroproliferative disorientation during the wound-healing process (Shaheen, 2017; Sidle & Kim, 2011). They can grow over time extending beyond the initial site of injury, rarely regress, and tend to recur after excision. In addition, extensive keloidal scars are aesthetically disfiguring and sometimes associated with pain, itchiness, and discomfort. In some cases, a patient's quality of life is affected by the physical and psychological impacts of the scars (Robles & Berg, 2007).

The pathogenesis of keloids has yet to be known properly up to this day and many theories have been described in various studies. Therefore, there is no ideal treatment for keloids, and managing these scars must be tailored to the individual patient. It is very challenging for physicians when it comes to keloid management because of the availability of various treatment modalities. Steroid injection is known to be the most common and first-line treatment regimen for keloid, but its usage has limitations due to side effects. Other effective therapies are adhesive tape supports, silicone-based products, pressure therapy, surgical excision, cryotherapy, radiotherapy, laser therapy, 5-fluorouracil (5-FU) , and imiquimod. In addition, there are emerging therapies such as interferon, bleomycin, mitomycin C, botulinum toxin type A, tamoxifen, growth factors, ACE inhibitors, calcium channel blockers, light therapy, stem cells therapies, and genetic and epigenetic therapies. However, steroid injection and silicone gel sheet treatment have been prioritized in most cases (Barone et al., 2021; Robles & Berg, 2007; Shaheen, 2017; Sidle & Kim, 2011). Lately, laser treatment in keloids has become an interest to physicians because of its better

outcomes, and studies are conducted to compare its efficacy with other treatment options. Studies have found that post-treatment results and patient satisfaction after treating with a combination therapeutic approach, for instance, laser treatment plus steroid injection, outnumber the monotherapy regime (Al-Attar, Mess, Thomassen, Kauffman & Davidson, 2006).

Laser therapy is one of the options being widely used at the current time for keloid scars and there are vascular lasers, ablative, and non-ablative lasers available to opt for the treatment. However, most of the previous studies compare the combined therapy (laser plus other treatment modalities) with a monotherapy regime. This systematic review is to describe the efficacy of three different lasers (585-595 nm Pulsed Dye Laser, 1064 nm Nd: YAG laser, and 10600 nm fractional CO_2 laser) in treating keloids either in combination therapy or laser alone therapy.

1.2 Research Objectives

1.2.1 To provide dermatologists with an overview of the available information on current laser treatment options for keloid scar

1.2.2 To compare the efficacy of 585-595 nm Pulsed Dye Laser, 1064 nm Nd: YAG laser and 10600 nm fractional CO_2 laser used in the treatment of keloids.

1.3 Research Questions

What is the efficacy of 585-595 nm Pulsed Dye Laser, 1064 nm Nd: YAG laser, and 10600 nm fractional CO_2 laser machines in treating keloid scars?

1.4 Research Framework

After framing the answerable research question, a systematic search of the literature associated with the laser treatment of keloids from reliable electronic-based data sources (PubMed, Cochrane Library, and SCOPUS) was carried out. The collected randomized controlled trials, prospective and retrospective studies were screened and excluded according to the determined eligibility criteria, and a systematic review was performed step-by-step using the PRISMA guideline. The

outcomes were integrated narratively by drawing up a detailed table describing every study that had been reviewed in detail.

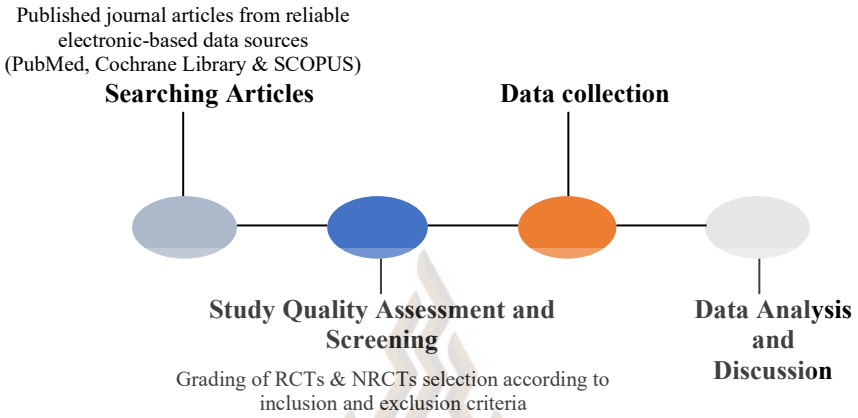

Figure 1.1 Research framework

1.5 Definition of Terms

Vancouver Scar Scale (VSS) was first designed by Sullivan, Smith, Kermode, Mclver, and Coutremanche in 1990 and has been applied to assess the quality of the scar which consists of four parameters: scar height and thickness, pigmentation, pliability, and vascularity. The total score range is from 0 to 13 points, which combines subscales under each category. A score of 0 can be assumed as normal skin whereas a score of 13 represents the worst scar condition.

Table 1.1 The Vancouver Scar Scale (VSS)

Scar Characteristics	**Score**
Vascularity	
Normal	0
Pink	1
Red	2
Purple	3
Pigmentation	
Normal	0
Hypopigmentation	1
Hyperpigmentation	2
Pliability	
Normal	0
Supple	1
Yielding	2
Firm	3
Ropes	4
Contracture	5
Height (mm)	
Flat	0
<2	1
2~5	2
>5	3
Total score	13

Source: Sullivan,1990

Fitzpatrick Skin Phototype classifies the skin color and the skin's reaction to sun exposure either burn or tan. The following table can be applied to determine the skin type scientifically.

Table 1.2 Fitzpatrick Skin Phototype

Skin type	**Typical features**	**Tanning ability**
I	Pale white skin, blue/green eyes, blond/red hair	Always burns do not tan
II	Fair skin, blue eyes	Burns easily tans poorly
III	Darker white skin	Tans after the initial burn
IV	Light brown skin	Burns minimally, tans easily
V	Brown skin	Rarely burns, tans darkly easily
VI	Dark brown or black skin	Never burns always tans darkly

Source: Gupta, 2019

Chapter 2

Literature Review

2.1 Keloids

Keloid is a pathological scar that represents a deviation from the normal wound-healing process and is also known as a benign fibroproliferative disorder. Unlike hypertrophic scars, keloids tend to grow beyond the original wound border, continually growing, and have a high rate of recurrence after excision. The associated symptoms are pain, itchiness, burning sensation, hyperesthesia, and movement limitation if occur over the joint. The most concerning problem that patients seek for treatment is cosmetic purposes especially if the keloid is in the exposed area and when the lesions become insufferably itchy. Keloids are esthetically unpleasing, and they have a lot of impact on the patient's quality of life. It was demonstrated that individuals with abnormal scars have an equal reduction in the level of quality of life as psoriasis patients (Limandjaja, Niessen, Scheper & Gibbs, 2020).

Since the pathogenesis of keloid is poorly understood, there is no proper protocol or ideal treatment option, and prevention is the key step in high-risk patients. Therefore, it is very challenging for clinicians to achieve a complete resolution for the keloid. A wide variety of treatment options are available, and treatment must be tailored according to each patient. Treatments for keloids include surgical excision, corticosteroids injection, and other intralesional therapies: 5-fluorouracil (5-FU), bleomycin, verapamil, and interferon; silicone gel sheeting, topical imiquimod, pressure therapy, cryotherapy, radiation, laser, and light-based therapies (Barone et al., 2021; Ojeh, Bharatha, Gaur & Forde, 2020). However, it has been challenging to determine which of the available treatment modalities may be considered the best treatment option due to the dearth of high-quality, controlled comparative trials. Intralesional corticosteroid injection has mostly been stated as the first line of treatment, but it has limitations to use for the long-term owing to its side effects. Silicone gel sheets also show an effective result for minor keloid scars, but they must

be worn for at least 12 hours daily and patient compliance is important to achieve the expected result (Al-Attar et al., 2006). In most cases, a combination therapeutic approach gives better results and patient satisfaction than monotherapy. Recurrence is common, even with combination therapy.

Laser therapy is one of the options being widely used at the current time for keloid scars. Lasers have introduced new ways to manage keloids that may result in improved aesthetic and symptomatic outcomes and decreased keloid recurrence. However, when it comes to laser therapy, there are various kinds of laser machines, and each machine has its pros and cons as well as different outcomes. In some studies, the optimal laser is said to be the 585 nm PDL and on the other hand, promising results can also be achieved with the 1064 nm Nd: YAG laser and 10600 nm fractional CO_2 laser. Laser treatment should be carried out as early as possible for better results, especially in individuals who are prone to keloid scars.

2.1.1 Epidemiology and Genetics

Keloid has varying prevalence for different populations, and it is said to have a higher prevalence among African Americans, and Asians, and a lesser degree in Hispanics and Mediterranean descent. Studies have found that darker skin populations are likely to have keloid 15 times more than fair skin individuals (Sidle & Kim, 2011). Keloids are between 4.5% and 16% more common in blacks and Hispanics during puberty and pregnancy which was explained by the hormonal influence (Chike-Obi, Cole & Brissett, 2009; Murray, 1994). Although there is no significant difference between males and females, it is reported that there is slight female predominance which may be due to ear piercing and cosmetic concerns.

Keloid can occur at all ages; however, it is most likely to take place between 11-30 years. A study in Chinese Han patients showed that the peak age of onset was 10-19 years in females and 20-29 years in males (Lu, Zheng, Yao & Zhang, 2015). Recent data are providing that keloids are more prone in patients after head and neck surgery, and women after cesarean section, and the incidence rate is gradually increasing in African Americans in comparison with Caucasians and Asians (Young,

Worsham, Joseph, Divine & Jones, 2014). According to one study on Asian people, the annual incidence rate of keloids is 0.15% in the overall population: 0.19% in women, and 0.12% in men. These findings suggest that Asians have an incidence rate of keloids that is comparable to Caucasians but lower than Africans. (Sun, Wang & Lee, 2014).

A genetic component may play a role in the increased risk of keloid in some ethnic groups. The host genetic variables on disease initiation were influenced by a positive family history of keloid. Genome-wide association research revealed that some individuals have an autosomal recessive inheritance pattern while others have an autosomal dominant inheritance mode, both of which have variable expression and insufficient clinical penetrance (Murray, 1994; Wang, Huang, Horng, Yeh & Chen, 2018). Keloid susceptibility genes have not been discovered yet which is due to genetic heterogeneity, in which different genes contribute to the development of keloids in different families (Robles & Berg, 2007). One significant familial investigation found susceptibility loci on chromosomes 2 and 7. Most cases are random and lack any discernible patterns of hereditary. The bulk of keloids is therefore unlikely to be caused by a single potential gene (Chike-Obi et al., 2009).

In addition, keloid development has been linked to rare diseases like Rubinstein-Taybi and Goeminne Syndrome. Other dermatological conditions such as scalp dissecting cellulitis, acne vulgaris, acne conglobata, hidradenitis suppurativa, pilonidal cysts, and responses to foreign bodies are said to be associated with keloid formation as well. It is also reported that keloids are related to some connective tissue disorders like pachydermoperiostosis, scleroderma, and Ehlers-Danlos syndrome (Murray, 1994).

2.1.2 Causes and Clinical Features of Keloids

Keloids occur in predisposing individuals following accidental or incidental procedures. Along with more evident injuries such as earlobe piercing, lacerations, or surgical wounds, keloids are frequently described as being caused by acne, folliculitis, chicken pox, and immunizations. After injury or inflammation, keloids can start to

form as soon as 1 to 3 months later, while some can take up to a year (Robles & Berg, 2007).

Skin tension is considered a critical local factor when it comes to keloid formation. Hypoxia, endocrine dysfunction, and fatty acid, autoimmune and genetics are predisposing factors for keloid, as well as blood type A, Hyper IgE, hormonal peaks during pregnancy or puberty, are reported as additional risk factors (Murray, 1994; Ojeh et al., 2020).

Anatomic locations that have a higher propensity for keloid are the upper back, shoulders, back of the neck, anterior chest, upper arms, and earlobes. Chike-Obi et al. reported an incidence rate of the pre-sternal region (34%), deltoids (17%), upper limbs (13%), and lower limbs (10%), as well as the ear (9%). Although the cause of site specificity is unknown, excessive skin tension and mechanical stress are commonly acknowledged. Earlobe keloids, an exception to the high skin tension hypothesis, are thought to develop in areas of minimal tension as a result of the expansion of trapped dermal elements in persons who are prone to getting keloid following an injury (Chike-Obi et al., 2009). Massive keloid rarely develops on the palms and soles areas where we would anticipate tremendous skin stress (Robles & Berg, 2007).

Keloids can be seen as raised, firm fibrotic masses often associated with pruritus (86%) and pain (46%). Keloid in Caucasians exhibits erythematous and telangiectatic while keloids in darker skin tend to be hyperpigmented (Chike-Obi et al., 2009). They grow gradually over the border of the original site and never regress. The term “Keloid” originated from the Greek word defined as “crab claw-like” because of its claw-like extension appearance and growth horizontally to invade the surrounding skin. Keloids are mainly divided into two phenotypes: ‘superficial spreading or flat keloids’ and ‘bulging or raised type’ (Limandjaja et al., 2020). The shapes of keloids vary depending on where they are located such as butterfly shape on the shoulder, crab claw shape on the anterior chest, and dumbbell on the upper arm (Ogawa, 2022).

2.1.3 Wound Healing Process

The skin undergoes a repair process when there is a disruption to the skin integrity to restore its function. The normal wound healing process comprises four steps including hemostasis, inflammation, proliferation, and remodeling. Keloid is one of the results of the abnormal wound-healing process.

Hemostasis is the initial step of wound healing and takes place by platelet aggregating to the injured site and occurs immediately within minutes after the insult. These platelets cause degranulation and there are releases of cytokines, chemokines, and growth factors forming a clot. These chemokines and cytokines attract the inflammatory cells and thus neutrophils are the first cells to arrive at the site which is followed by macrophages and lymphocytes orchestrating the inflammatory phase. Inflammation is the key phase in wound healing since disruption or prolongation of this phase can result in impaired healing, chronic wounds, and more scarring. The hemostasis and inflammatory phases require 72 hours to complete.

As soon as the inflammatory phase is complete, the proliferation phase begins, characterized by the accumulation of fibroblasts, keratinocytes, and endothelial cells. A clot formed in the hemostatic phase is replaced by a granulation tissue composed of an extracellular matrix (ECM) including proteoglycan, collagen, hyaluronic acid, and elastin. Many inflammatory mediators such as transforming growth factor (TGF), vascular endothelial growth factor (VEGF), and interleukin take part in this step, and this phase processes for days to weeks.

The apoptosis of existing cells and the generation of new cells must be precisely balanced during the remodeling phase. This phase, which lasts for a few months to years, is crucial for the gradual breakdown of the abundant ECM and immature type III collagen, and the production of mature type I collagen. Any deviation at this stage could result in an excessive rate of wound healing or a chronic wound. Age affects a person's capacity to heal wounds with no excessive healing. The likelihood of excessive wound healing increases with increasing age (Gantwerker & Hom, 2011; Wang et al., 2018).

2.1.4 Pathogenesis of Keloid

Even though the pathogenesis of keloidal scar is not fully understood, clinical evidence suggests that it is an aberrant form of wound healing that may be caused by dysregulation in one of the four phases of the normal healing process and is characterized by persistent localized inflammation.

There are many hypotheses postulated to be the cause of keloid which include the tension hypothesis, imbalance collagen turnover, cytokines and growth factor overexpression, and sebum reaction theory. Excessive fibroblastic response and ECM accumulation are said to be most associated with excessive wound healing. Ojeh et al. also stated the following as pathogenesis of keloid: increased cutaneous fibroblast proliferation and decreased apoptosis, increased collagen fiber formation, altered production and remodeling of the extracellular matrix as well as several cytokines, growth factors, and proteolytic enzymes (Ojeh et al., 2020). Moreover, Gantwerker and Hom supported the fact that keloids develop because of excessive deposition of ECM (water and glycoproteins), and type III immature collagen. Given that keloid tissue has increased TGF-β mRNA expression, TGF-β appears to play a significant role in the development of keloid lesions as well (Gantwerker & Hom, 2011).

2.1.4.1 Tension Theory

According to tension theory, mechanical strain predisposes to the misalignment of healing wounds. Mechanical tension influences collagen architecture and orientation, collagen production, and dermal remodeling. Through a variety of routes, such as the TGF-β pathway or the NF-κB pathway, tension converts mechanical inputs into chemical signals. By influencing the production of associated proteins, tension encourages the growth of fibroblasts and the formation and accumulation of collagen fibers to generate pathological scars (Ogawa et al., 2012).

2.1.4.2 Sebum Reaction Theory

Sebum reaction theory explains that when a person has a dermal injury, the pilosebaceous unit is exposed to the systemic circulation, and in those who retain T lymphocytes that are sensitive to sebum, a cell-mediated immune response is

triggered. The chest wall, shoulder, and pubic area are among the anatomical regions where keloids are more likely to develop because of high concentrations of sebaceous glands (Al-Attar et al., 2006).

2.1.4.3 Imbalance Collagen Turnover

Abnormal regulation of the collagen equilibrium is considered to play an important role in keloid formation. Excessive wound healing is a result of aberrant collagen turnover and excessive collagen synthesis, which are brought on by the dysregulation of matrix-degrading enzymes. TIMPs can block MMPs by attaching to the zinc-binding domain of functional MMPs or to the pro-MMP zymogen, which demonstrates the activation process. An imbalance of MMP and TIMP causes aberrant wound healing because they jointly regulate the synthesis and breakdown of ECM at wound sites which explains collagen metabolism and MMP regulation are useful targets for therapeutic therapies (Al-Attar et al., 2006; Wang et al., 2018).

The tissue mass in keloid is determined by increased ECM and water in which chondroitin sulfate was found as the main glycoprotein. In newly formed keloid, hyperactivity of prolyl hydroxylase points out increased collagen synthesis and these collagens are said to be different from normal skin. Type III collagen is synthesized in increased amounts with varying degrees. When the ratio of type I to type III collagen is compared to that of normal skin, the number dramatically increases in keloid tissue. In addition, keloid collagen is tested to be easily soluble in acid, suggesting keloid collagen's instability. Other investigations have noted this high acid solubility as a decrease in complex collagen crosslinking. Therefore, keloid collagen is less mature and less stable than normal skin. (Murray, 1994).

2.1.4.4 Growth Factor Overexpression

Regarding growth factor involvement, TGF-β and PDGF concentrations appear to be elevated in the keloid tissue, probably due to the high expression of their receptors. TGF-β increases collagen deposition and extracellular matrix (ECM) by stimulating the fibroblasts. In addition, it activates the synthesis of PDGF which regulates the rate of granulation tissue development and promotes collagen production

in the later stages of the wound healing process. Moreover, TGF-β controls the enzymes that change and deteriorate the ECM of the scar, and lower concentrations of plasminogen activator, collagenase, and MMPs could further explain why keloids fail to show scar regression (Sidle & Kim, 2011).

Chike-Obi et al.(2009) also reported that type I procollagen is overproduced, and VEGF, TGFβ-1, TGFβ-2, and PDGF are expressed at higher quantities. On the other hand, there are lower levels of apoptosis and downregulation of genes such as p53. In addition, they mentioned there are abnormalities in the connexins, which are crucial for the development of gap junctions. Reduced connexin expression and decreased gap junctional intercellular communication make it difficult to exchange inhibitory signals, which may cause programmed cell death to occur more slowly than usual.

They also explained how hypoxia is one of the causative factors in keloids. Keloid fibroblasts experience a relatively hypoxic state because keloid tissue is more metabolically active and uses more oxygen than normal scar tissue. Low oxygen diffusion and this high oxygen consumption potential may be factors in the pathophysiology of keloid development. Last but not least, they added that mast cells and histamine are present in keloid tissue, particularly early in the clinical course, which explains why keloids are itchy (Chike-Obi et al., 2009).

2.1.5 Keloid vs Hypertrophic Scars

Keloid and hypertrophic scars are two examples of excessive wound healing that have been reported. Although these two abnormal scars are fibroproliferative skin disorders, they have variable degrees of inflammation. Dr. Ogawa termed “keloid” as a pathological process that is strongly inflamed and “hypertrophic scar” as a pathological process that is weakly inflamed (Ogawa et al., 2016; Wang et al., 2018).

Keloids need to be differentiated from diseases that have clinical resemblances such as a hypertrophic scar, dermatofibroma, lobomycosis, dermatofibrosarcoma protuberans, trichilemmal carcinoma, and keloidal basal cell carcinoma. Hypertrophic scars, which are also known as pseudo-keloid are the primary diagnosis of keloid and

it is essential to differentiate the scars since appropriate treatment options are selected depending on the scar type.

The clinical trait of escaping the initial boundary of injury and invading the adjacent normal skin is used to make the diagnosis of keloid. Clinically, keloid nodules have lustrous, supple surfaces and range in firmness from soft and doughy to rubbery and rigid. Hair follicles and other functioning adnexal glands are typically absent from lesions. Early lesions are frequently erythematous, but as the scars age, they turn brownish-red and pale. Most lesions enlarge from weeks to months, while some keep increasing in size for years. Keloids typically grow slowly, but on rare occasions they can grow quickly, tripling in size in a matter of months. The keloids on the abdomen, neck, and ears are typically pedunculated. Most keloids have typical round, oval, or rectangular shapes with their margins, however, some have claw-like structures with irregular margins.

In contrast, hypertrophic scars stay within the original wound boundary and are usually erythematous in color. A hypertrophic scar develops quickly after an injury or surgery and is in line with the extent of the damage. With time, it began to naturally flatten (Muir, 1990; Munro, 1995; Robles & Berg, 2007; Shaheen, 2017).

In histological features, diagnosis is based on the thick eosinophilic collagen bundles called keloidal collagen (Ogawa et al., 2016). Keloidal collagen appears as whorls and hyalinized collagen bundles and this collagen with uneven orientation is different from normal tissue. Moreover, keloidal collagen was infrequently observed in hypertrophic scars. While hypertrophic scar and keloid both have high fibroblast density, only keloid exhibits elevated fibroblast growth rates. In contrast to hypertrophic and normal skin, keloid scars include disorganized type I and type III collagen (Al-Attar et al., 2006; Wang et al., 2018). According to some studies, the following four histological findings favored keloid: absence of prominent vertically oriented blood vessels, presence of keloidal hyalinized collagen and tongue-like advancing edge underneath normal appearing epidermis and papillary dermis, a horizontal cellular fibrous band in the upper reticular dermis and a prominent fascia-like band (Ojeh et al., 2020; Robles & Berg, 2007).

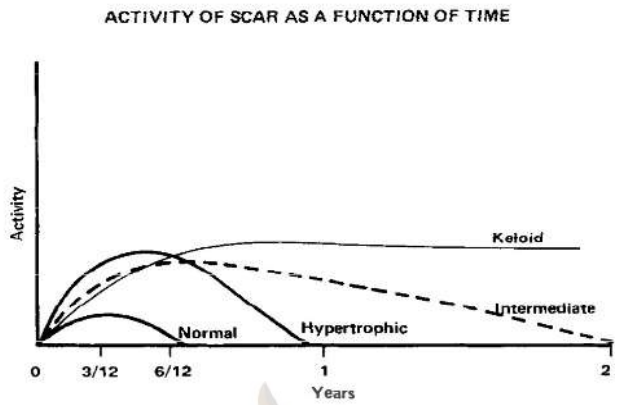

Figure 2.1 The activity of various scar forms over time

Source: Muir,1990

2.2 Treatment of Keloids

Despite a growing understanding of the pathology of keloid scars, no single treatment is consistently beneficial, and a variety of methods have been described with varying degrees of efficacy. Treatment for keloid scars can be challenging, and traditional silicone gel and corticosteroids frequently don't work. A high degree of recurrence has been observed with monotherapy using several techniques, including surgical excision, intralesional steroid injections, and silicone sheath application. Additionally, some of these therapeutic options, such as radiation therapy, and repeated high-dose intralesional steroid injections, are known to have long-term negative effects. The absence of data-driven therapy pathways and the dearth of effectively established and implemented treatment protocols as well as well-conducted clinical trials that would serve as the cornerstone for proper clinical management of patients with various types of keloids appear to be the biggest barriers to the development of optimal treatment for patients with keloids.

Regarding the meeting report of the 3rd international symposium of The Keloid Research Foundation (KRF), KRF recommended the following treatment methods: (i) intralesional triamcinolone, (ii) intralesional chemotherapy, (iii) cryotherapy and (iv) pressure devices. KRF does not favor performing surgery, radiation therapy, and laser treatment without adjunctive therapies. This means the foundation stressed the point of reducing the risk of the iatrogenic worsening of the

keloids. Additionally, future advancements in the fields of surgery, radiation, and laser therapy in conjunction with emerging targeted therapeutics may offer a multidimensional strategy for treating keloids (Uitto & Tirgan, 2020).

Due to the wide array of treatment regimens and the high recurrent nature of keloid, it is challenging for clinicians to cure the lesions completely. The treatment is tailored to individual patients according to the location, size, and depth of the lesions, the age of the patient, and the previous treatment response. Another important point to be considered while choosing an option is the duration of the scar. Recently occurred lesions come out with a better result, and it is said that keloid more than a decade has a risk of cancer and requires close management.

2.2.1 Corticosteroid

Injecting a corticosteroid into the lesion is accepted as first-line therapy but long-term usage can cause serious adverse effects and therefore it has limitations. Triamcinolone acetonide (TA) is commonly used for treating keloid due to its anti-inflammatory, anti-proliferative, and vasoconstriction effects. Corticosteroids are considered to enhance the characteristics of keloids by promoting collagen degradation, inhibiting fibroblast growth, and inducing apoptosis in fibroblasts. They also appear to suppress TGF-β1 expression (McCoy, Diegelmann & Cohen, 1980).

The recommended dose is 10-40 mg/L of TA administered intralesional at four to six weeks intervals. The reported response rate varied from 50-100% with recurrence rates of 9-50% in completely resolved scars if it was used as a single modality. The better number was seen when combined with excision showing a recurrence rate of less than 50%. Complications of repeated corticosteroid injections include atrophy, telangiectasia formation, and pigmentary alteration, especially in skin type V and VI patients. A success rate of 70% was experienced when combined with 5-Fluorouracil (50mg/ml 5-FU in 10mg/ml TA) (Shaheen, 2017). It is challenging to treat particularly big or numerous keloids with intralesional injection due to the discomfort of the procedure and worries about repeatedly injecting high dosages of corticosteroids (Robles & Berg, 2007).

2.2.2 Silicone Gel Sheeting

Silicone gel sheeting is reported to have an 80% success rate in preventing recurrence after excision. The flattening of the keloid is not due to the silicone effect itself, but it is assumed to be the result of the occlusion and hydration of the sheet. The sheet must be worn for 12 to 24 hours per day for 2-3 months to yield the desired effect. There are varying results with this treatment and patients' compliance is essential since they must wear the sheet for a long time (Chike-Obi et al., 2009; Shaheen, 2017).

2.2.3 Surgical Excision

Simple surgical excision is usually followed by a recurrent rate of 45%-100% unless adjunct therapies are employed. The surgeon who operated should pay close attention not to put too much tension while closing the wound and abnormal tissue should be well-executed (Elsaie, 2021). Alster and Tanzi reported that in one study, there was a 64% improvement in 24 keloid patients who were treated with core extirpation which is a novel technique comprising the removal of the fibrous core without executing the shell of the keloid to form a flap (Alster & Tanzi, 2003).

2.2.4 Cryotherapy

Liquid nitrogen medium in the cryogen spray freezes and ablates the targeted lesions through the mechanism of damaging the microvasculature and circulatory stasis leading to anoxia with eventual necrosis. A treatment session of 1 or 2 freeze-thaw cycles lasting 20-30 seconds every 20-30 days is required to obtain the desired result. Data showed that there was total resolution with no recurrence in 51-74% of patients after 30 months of observation. Intralesional cryoprobe gain flattening of keloid in 75% of patients and 67.4% reduction in scar volume in earlobe keloids (Shaheen, 2017). Nevertheless, cryotherapy works better with small lesions, and pain during treatment causes poor patient compliance as well as hypopigmentation in darker-skinned patients attributing to less favorable use of this method (Alster & Tanzi, 2003; Chike-Obi et al., 2009). One review stated that there was another evident use of cryotherapy as an anesthetic in the treatment of keloid lesions by utilizing a

cryotherapy probe before steroid injections revealing a statistically significant decrease in pain (Limmer & Glass, 2020).

2.2.5 Radiotherapy

Radiation damages the fibroblasts in the wound inhibiting neovascularization, and ultimately reducing collagen formation. The effectiveness of radiotherapy in combination with the surgical method is 80% which is the same as with injections of corticosteroids. The lack of a defined radiation dose, energy, or timing makes it challenging to compare results from different research. If the radiation was given within 48 hours of excision dosing 10-20 Gy over 2-4 days, a satisfactory outcome will be seen. Skin hyperpigmentation and a cancer-causing effect are adverse reactions to this treatment. Cancer-related issues are the primary reason to avoid using radiation in treatment that does not endanger life. Radiotherapy is always reserved as the last resort if only the lesions no longer respond to any other methods (Chike-Obi et al., 2009; Shaheen, 2017).

2.2.6 Pressure Therapy

Compression therapy was introduced a long time ago and its continuous pressure is thought to reduce the size and thickness of the lesion via tissue ischemia, decreasing tissue metabolism and increasing collagenase activity. Another postulation is that MMP-9 or PGE2 was released when pressure was exerted, and extracellular matrix remodeling softened the scar. One of the disadvantages of this modality is that patients need to wear the pressure dressing for 6 months minimum, 18 hours per day, and only effective in younger scar (< 12 months). In addition, the expected outcomes will not be achieved if it is worn at joints due to frequent movement (Alster & Tanzi, 2003). Ho Jun Lee and colleagues reviewed that there are no comparable evaluations of pressure amount, and the pressure amount employed in clinical settings is based on empirical reports. The suggested range currently is 15-40 mmHg for more than 23 hours a day for at least six months (Lee & Jang, 2018).

2.2.7 5-Fluorouracil

5-Fluorouracil, the pyrimidine analog, which was used as antimetabolite in chemotherapy, reduces fibroblastic growth and is thought to lessen postoperative scarring by reducing fibroblast proliferation. According to a prior study, 85% of keloids displayed >50% improvement after receiving 7 treatments of once-weekly intralesional 5-FU (50 mg/mL) with a 47% recurrence rate within a year (Shaheen, 2017). Chike-Obi et al. reviewed that flattening of keloid was witnessed in all participating patients and a greater response was seen even in 5-year-old scars. However, better results were seen when used adjunctly with pulsed dye laser treatment or intralesional corticosteroid. Adverse effects of 5-FU include pain, burning sensation, hyperpigmentation, and ulceration at the injection site (Chike-Obi et al., 2009).

2.2.8 Verapamil

In 1994, Lee and colleagues introduced intralesional verapamil, a calcium channel blocker, for the treatment of burn scars (Lee, Doong & Jellema, 1994). Verapamil exhibits anti-fibrotic properties that may be beneficial for keloid and hypertrophic scars (Kant, Kerckhove, Cella, Tuinder, Hulst & Grzymala, 2018). Verapamil seems to work by inducing pro-collagenase expression and increasing collagenase. Moreover, it inhibits the synthesis of extracellular matrix molecules such as collagen, fibronectin, and glycosaminoglycans (Verhiel, Grzymala & Hulst, 2015). The elevation of interleukin-6 (IL-6) expression was found in keloid fibroblasts, and verapamil inhibits the production of IL-6 and vascular endothelial growth factor (VEGF).

In a study of 40 patients with 48 scars where the efficacy of intralesional triamcinolone acetonide and verapamil was compared, the reduction in scar height was accompanied by an improvement in scar vascularity and pliability, in both groups. However, after 24 weeks of observation, only 60% of the scars in both groups were able to regain their original pigmentation. As a substitute for triamcinolone in therapy, verapamil is nearly as beneficial and provides a range of options (Ahuja & Chatterjee, 2014). In a meta-analysis comparing the efficacy of corticosteroids and

verapamil,the effectiveness of scar recovery was more pronounced with triamcinolone acetonide compared to verapamil. However, the study found that verapamil exhibited a less severe adverse effect than triamcinolone (Kuang, An & Li, 2021).

2.2.9 Bleomycin

Bleomycin was first discovered from the fungus *Streptomyces verticillus* by Umezawa and colleagues in 1962. It is widely used to treat a variety of cancers as an anti-tumor agent. Furthermore, dermatologists treat resistant warts, hypertrophic scars, and keloids using bleomycin (Yamamoto, 2006). Bleomycin can cease the synthesis of DNA and RNA, drive fibroblasts to undergo apoptosis, and reduce collagen formation (Saitta, Krishnamurthy & Brown, 2008). In a study where intralesional bleomycin injection was performed in keloid scars of the Vietnamese population, 70.8% of scars became completely flattened. However, undesirable effects such as pain(100%), blisters(78.3%), ulceration(5.8%), and hyperpigmentation (56.7%) were reported. This study had a significant recurrence rate, with 50% occurring 18 months after the last therapy session. (Huu et al., 2019).

2.2.10 Laser Therapy

Over the past 30 years, attention has been drawn to laser therapy, a new less invasive medical procedure to offer a more comfortable treatment alternative. The use of several lasers has demonstrated therapeutic and aesthetic advantages for patients. The fundamental idea behind lasers is based on interactions between the laser and tissue that are photothermal, photochemical, and photomechanical. Dermatological laser therapy aims to induce photothermal effects, which are heat-based and direct energy to certain target chromophores in the skin while minimizing harm to surrounding tissue or structures which is also known as selective photothermolysis. Non-ablative and ablative fractional devices, which are more tolerable than ablative 10600 nm Carbon dioxide (CO_2) and 2940 nm Erbium-doped yttrium aluminum garnet (Er: YAG) lasers, have been created via further advancements in laser technology. One review stated that the earliest lasers used to treat keloids were continuous wave argon, CO_2, and Nd: YAG lasers (Khatri, Mahoney & McCartney, 2011).

Numerous aspects of the scar characteristics including its color, texture, duration, and prior treatments have an impact on the laser and treatment parameters. To select the best course of laser therapy, it is crucial to correctly classify the type of scar at the initial inspection. (Khatri et al., 2011; Lupton & Alster, 2002).

2.2.10.1 585 - 595 nm Pulse Dye Laser (PDL)

The exact mechanism of action of how PDL irradiation heals proliferative scars is not known. It is based on selective photothermolysis where hemoglobin absorbs light energy, creating heat and causing coagulation necrosis resulting in fewer feeding vessels for keloid tissue. Additionally, hypoxia due to laser-damaged capillaries also alters collagen synthesis by fibroblasts and degradation through metalloproteinase release. Moreover, it has been demonstrated that irradiated scars include a significant number of local mast cells that can produce a variety of cytokines that may drive collagen remodeling (Nouri et al., 2010). On the other hand, Paquet and colleagues stated laser reduces the mast cell number since fibroblast activity is stimulated by histamine (Paquet, Hermanns & Pierard, 2001).

Fitzpatrick skin type I and II patients are a better candidate than darker skin types since they contain lesser melanin and chromophore which compete for laser absorption. Lower fluence should be utilized in dark-skinned individuals to avoid unwanted side effects, for instance, post-operative dyspigmentation. Alster and Handrick described the range of laser parameters for PDL to treat keloids as 6.0 to 7.5 J/cm^2 with 5 or 7mm spot size and 4.5 to 5.5 J/cm^2 with 10mm spot. They also recommended that 2-6 laser sessions are necessary to treat keloid with PDL. The favorable result in scar height reduction and texture, as well as the color of the scar, was reported and they mentioned neither recurrence nor scar worsening was detected in several years of follow-up (Alster & Handrick, 2000; Lupton & Alster, 2002).

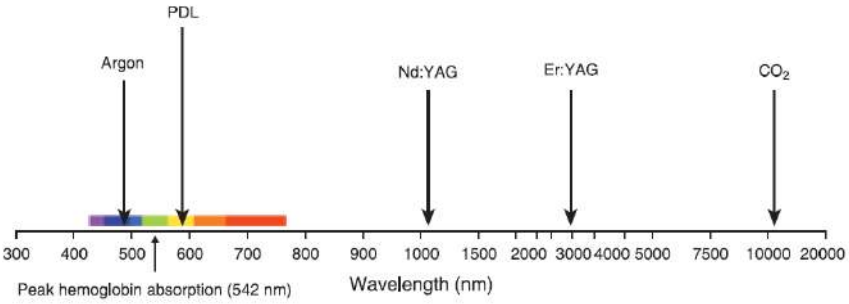

Figure 2.2 Shows different wavelengths of lasers. PDL, pulsed dye laser; Nd: YAG, neodymium: yttrium- aluminium -garnet; Er: YAG, erbium: yttrium-aluminium-garnet

Source : Bouzari, Davis & Nouri, 2007

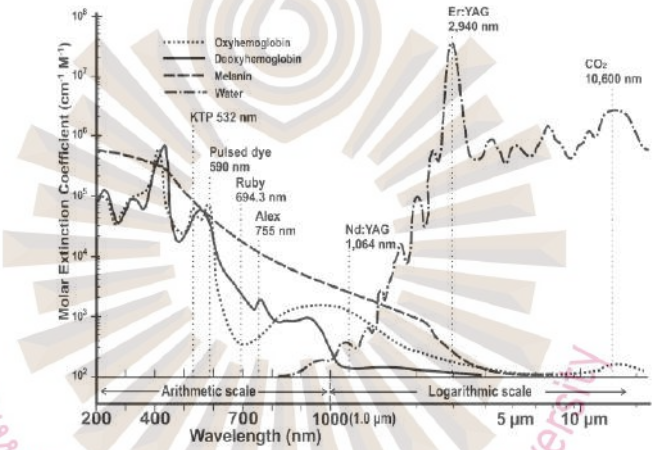

Figure 2.3 Absorption Spectra of chromophores at different wavelengths

Source : Omi & Numano, 2014

One study directly compared the two pulse durations (450μs and 1.5ms) of 585 nm PDL and reported that both pulse widths showed satisfactory improvement of VSS compared to the control. However, there were no prominent differences in results between short-pulse and long-pulse duration (Nouri et al., 2010). In another study, the researchers underwent treatment of post-thyroidectomy scar with 1.5ms and 10ms pulse duration of 585 nm PDL. As a final result, they saw that all parameters in VSS were improved apart from the thickness, and only pliability substantially improved following long pulse therapy compared to short pulse treatment (Lee et al., 2019).

Most of the studies supported the excellent outcomes of hypertrophic scars treated with PDL while this laser system does not yield expected satisfactory results in keloids since keloidal collagen is thicker and more hyalinized. Furthermore, PDL has an approximate 1.2mm depth of penetration, and efficacy in thicker keloids may be limited. PDL may also resolve scar-associated symptoms such as pruritus (Mamalis, Levtov, Nguyen & Jagdeo, 2014). Paquet and colleagues studied the effect of 585 nm PDL on the reduction of scar erythema in 11 patients who have skin phototypes II-IV, the mean scar duration was 4 years without prior scar treatment. They adjusted the parameters ranging from 6-6.5 J/cm^2 with 450ms pulse width using a 7mm spot size, and the treatment sessions varied from 1-3 times depending on the individual response. This study found that there was no significant difference in scar redness even after 3 laser sessions (Paquet et al., 2001).

Asilian and colleagues researched Triamcinolone acetonide injection combined with 5-FU and 585 nm PDL using 250μs pulse width at 5-7.5 J/cm^2 with a 5mm spot size for 3 sessions. The outcomes were described as 79% flattening of scar, improvement in pliability, decrease in scar erythema score, and greater itch reduction with high patient satisfaction (Asilian, Darougheh & Shariati, 2006).

Most of the research has been done on 585 nm, however, there are far fewer studies accessible on 595 nm. Regarding 595 nm PDL, a trial performed in Asian patients by comparing the two different pulse widths of 595 nm PDL which are 0.45 ms and 40 ms demonstrated that shorter pulse width produces a better result in reducing scar volume and softening of the scar. Additionally, they stated dark-skinned individuals, whose skin carries proportionately bigger quantities of epidermal melanin, benefit from vascular-specific lasers with a longer wavelength. The larger wavelength of the 595 nm laser is less absorbed by epidermal melanin than other wavelengths. In comparison to the 585 nm PDL, it thus produces less generalized damage to the pigmented epidermis (Manuskiatti, Wanitphakdeedecha & Fitzpatrick 2007).

2.2.10.2 1064 nm Nd: YAG Laser

In keloids, collagen was broken down and collagen formation was decreased by Nd: YAG laser-induced selective photothermolysis. The clinical reduction of keloids may also be influenced by the production of new normal collagen and the remodeling of collagen caused by thermal injury**.** While Nd: YAG therapy may share similar underlying mechanisms of action, it penetrates deeper into the body than PDL (Nischwitz et al., 2020; Ojeh et al., 2020; Said, Ghoneimy & Abdelshafy, 2022).

Apfelberg and colleagues studied the usage of Nd: YAG laser in plastic surgery and they elicited keloids aged over 2 years and are resistant to conventional therapy showed immediate shrinkage with a percentage of 5-8% in length, 7% in width, and 34% in height. Even though the keloid significantly shrank after the therapy, all keloids returned during the next 3–4 months. Later in the series, the treatment sites were additionally given topical steroids and intralesional steroids soon before or just after epithelialization (average 4-6 weeks). The outcomes were considerably enhanced as a result. This study mentioned that Nd: YAG laser provides a better result when combined with other treatment modalities, for instance, injection or topical steroids in this case (Apfelberg, Maser, Dds, White & Weston, 1984).

A prospective study was carried out by Kumar and colleagues on Indian patients with previously untreated keloid scars with size varying from 3-8 cm, and scar aging from 3-17 years. Laser parameters of spot size 0.5-1.0mm at 25-45watt power in 2-9 second pulse width non-contact mode had been set. The final observations were as follows; 58.8% of patients obtained a resolution after one session of laser treatment and follow-up for up to 5 years. 41.1% required a second session and the remaining 25-50% still needed steroid instillation even after the second laser treatment. This study also supports that Nd: YAG laser has a high recurrent rate if used alone and combination treatment provides better resolution and prolonged recurrent time (Kumar, Kapoor, Rai & Shukla, 2000).

2.2.10.3 10600 nm Fractional CO_2 Laser

Fractional photothermolysis is the newest innovation to hit the cutaneous laser market. It is a technique that involves thermally ablating a portion of the skin while keeping the surrounding normal skin unaffected. The undisturbed normal skin quickly fills in the columns of tissue that were initially removed. The array of microthermal treatment zones (MTZs) and tiny columns of thermal damage produced by fractional resurfacing devices pixilated light emissions into the skin. The healing process is faster with MTZs than with conventional ablative resurfacing. Moreover, fibroblast activity and neocollagenesis occur similarly to other laser resurfacing methods. Fractional photothermolysis is split into non-ablative and ablative fractional lasers. Ablative fractional resurfacing employs fractionated CO_2 and Er: YAG lasers to produce deeper columns of thermal damage (Khatri et al., 2011).

Fractional lasers also serve to assist drug delivery through the stratum corneum facilitating to increase the permeability of topical drugs. The MTZs created by a fractionated laser beam allow the passage of topical substances. The effectiveness of the drug is enhanced by improved skin penetration, which would also enable lowering dosages and a consequent reduction in adverse effects (La & Sg, 2016; Ng & Smith, 2022).

Al Janahi reported that the refractory keloid on the anterior and lateral neck, upper chest, and back of 72 years old African American man with Fitzpatrick skin type VI who did not respond to intralesional corticosteroid injection, PDL, and cryotherapy was successfully treated with fractionated CO_2 followed immediately by drizzling and injection of triamcinolone acetonide (Al Janahi et al., 2019).

In a study including 8 patients with a total of 12 keloids, MiXto SX fractional CO_2 laser applying 13 W of power, 8 SX of the index, and 40% coverage, 300µm spot diameter was used in combination with Same Plast Gel twice a day. After a total of 12 sessions per scar and follow-up for 1 year, they claimed the outcomes were optimal without recurrence (Scrimali et al., 2010).

In conclusion, keloids are burdensome and unpleasing scars and have a high impact on the patient's social life depending on the size and site of the lesions. Most of the lesions are asymptomatic, however pain and pruritus are reported. Hypertrophic scars are the main differential diagnosis of the keloid for different treatment options. Since the exact pathway for keloid formation is still under investigation, there is no gold standard treatment yet. Guidelines are postulated considering the scar characteristics and individual treatment response. Most of the studies claimed that intralesional steroid injection and silicone gel sheeting as first-line conventional treatments but there are limitations in prolonged usage due to side effects. Surgical excision alone has a high risk of recurrent and this can be improved by combining post-surgical radiation. However, radiotherapy is recommended only for resistant cases. Cryotherapy works better in small lesions, and it is one of the available options. Nowadays, with advancing technology in lasers, clinicians are using various laser machines widely and each type has its advantages and impact on the scar. The studies also support the use of laser machines in keloid therapy and the most popular laser is the 585-nm Pulsed Dye Laser. Nonetheless, keloid is tremendously difficult to attain a complete cure. Single therapy is inadequate and combination therapy always produces superior outcomes.

Chapter 3

Research Methodology

This chapter aims to provide detailed information on how this systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) 2020 checklist. Laser treatments are now widely used for keloid scars by most physicians and there are different types of laser machines available on the market. Both ablative and non-ablative laser machines are utilized in treating keloids, and information on their efficacy and outcome needs to be compared to support which laser machine is better for an individual patient.

3.1 Population and Samples

3.1.1 Study Population

Patients with keloid scars resulted from all possible causes irrespective of gender, age, ethnicity, or scar location, and patients with Fitzpatrick skin type I-VI.

3.1.2 Inclusion Criteria

Randomized controlled trials (RCTs), retrospective and prospective studies of laser therapy treating keloid scars using 585-595 nm Pulsed Dye Laser (PDL), 1064 nm Nd: YAG laser, and 10600 nm fractional CO_2 laser and these lasers being compared with a control group or other intervention, or no intervention. All the studies were only human studies and the English language articles from January 2010 to September 2023.

3.1.3 Exclusion Criteria

Articles covering other skin disorders or forms of scars, such as those that emphasize hypertrophic scars without discussing keloids, review papers, posters, oral presentations, editorials, and studies that did not assess or comment on the efficacy of the treatment method, and studies before January 2010 were excluded.

3.1.4 Types of Outcome Measures

Improvement in scar characteristics (vascularity, pliability, pigmentation, and height) according to validated scar scales, side effects, and recurrent rate.

3.1.5 Sample Size

We adopted the PRISMA flow diagram while collecting studies to match this systematic review's inclusion and exclusion criteria.

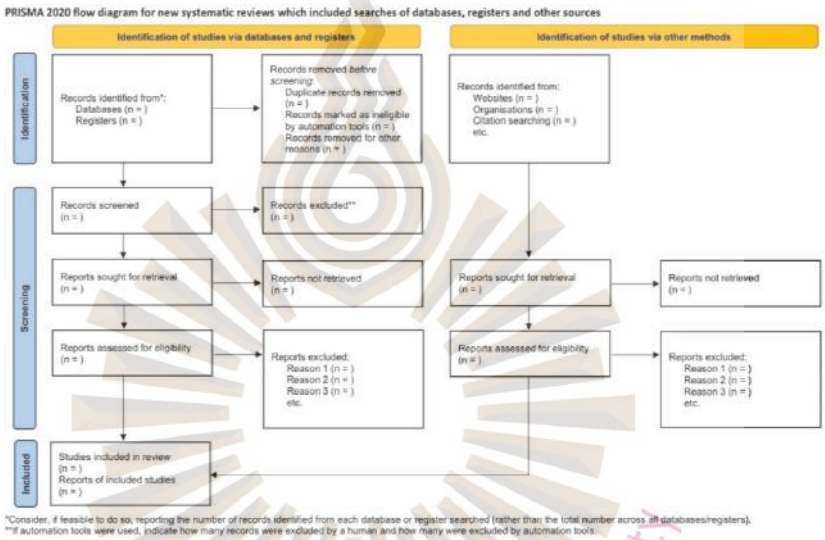

Figure 3.1 PRISMA 2020 flowchart illustrating the sequential application of inclusion and exclusion criteria to get the ultimate number of studies for the systematic review analysis

Source : Page et al., 2021

3.2 Research Instruments and Search Strategy

This systematic review was carried out according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) 2020 checklist (Page et al., 2021).

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Figure 3.2 PRISMA 2020 checklist

For this review, the following electronic databases were searched for RCTs, retrospective, and prospective studies.

a) PubMed
b) Cochrane Controlled Trials Register
c) SCOPUS

In addition, reference lists were manually scanned and searched for more valid studies by the snowball method. The list covered publications from 1st January 2010 up to the day we completed the search, which is 6 September 2023.

The MeSH terms we utilized were: “Lasers, Dye”, “Lasers, Solid-State”, “Lasers, Gas” linked with the keywords: keloid, keloid scar, carbon dioxide laser, pulsed dye laser and Nd:YAG laser using the Boolean searching (AND and OR). We put field tags such as [tw] and [tiab] behind each keyword so that search terms were involved in titles, abstracts, and text words. Truncation (*) was used to avoid the risk of bias due to spelling variations. The search strings varied according to the specific database. The detailed table for keywords and search strings used for each database is described in the Appendix.

Two researchers screened the articles manually using the help of software Zotero and Microsoft Excel. All studies resulting from Boolean searching of each database were recorded in Excel. Then both researchers manually screened the titles, sought duplicate articles, and removed them after the agreement. After removing the duplicate studies, titles, and abstract screening of the remaining studies were carried out. Papers that, according to their title or unclear abstract, we did not think should be excluded were tabulated and included for further screening stage.

After proper screening of titles and abstracts, articles were retrieved for full texts including both clear and unclear abstracts from initial screening. Required medical journals were obtained through PubMed, the Cochrane Controlled Trials Register, and SCOPUS in collaboration with the Institute of Dermatology and Rangsit University librarians. A list of the articles whose full texts could not be retrieved was created, and attempts were made to get in touch with the respective writers of these studies via email. Publications for which we were unable to acquire the full texts because the authors did

not reply were removed after two months. This is shown in a table with the title "Unretrieved Clear Studies" that is included as an appendix. Two trials had not been completed yet when we searched and that was also excluded with the reason of "Ongoing trial".

The full texts of the publications that we were able to collect were examined to ensure that they satisfied the established inclusion criteria. Studies that satisfied the inclusion criteria were included in the subsequent screening process, while those that did not were eliminated with an explanation for their exclusion. Furthermore, the reference lists of included studies were manually screened by two reviewers, and the title, abstract, and full-text articles searched were done in a similar manner as above. However, no further studies were added from the hand search of citations. The detailed record of study screening was described in the next chapter on the PRISMA flow diagram.

Any disagreement on the inclusion of studies was discussed between the two reviewers and critical appraisal and quality assessment of included studies were done independently.

3.3 Quality Assessment of Included Studies

The quality of each study was evaluated using the relevant tools based on the type of study. In this review, the level of evidence for all studies was determined using an Oxford Centre for Evidence-Based Medicine levels of Evidence 2011, when the risk of bias was assessed by using RoB2 for RCTs and the Newcastle-Ottawa Scale for NRCTs.

RoB2 quality assessment tool includes the following domains: the risk of bias arising from the randomization process, deviations from the intended interventions subcategorized into effect of assignment to intervention and effect of adhering to intervention, missing outcome data, risk of bias in the measurement of the outcome and selection of reported result. The overall risk of bias was assessed, and if any one of the domains demonstrated a high risk or there were multiple domains with some concerns, it was a high risk of bias. Then any one of the domains demonstrated some concerns, it

is considered to have some concern and lastly, if all the domains demonstrated a low risk, it was considered to have a low risk of bias.

On the other hand, the Newcastle-Ottawa Scale (NOS) was created to evaluate the quality of non-randomized studies (cohort and cross-sectional studies). NOS consists of three major perspectives: the selection of the study groups;the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively. Each category was rated by a star system and the total score determined the quality of study by good, fair, or poor. No further studies were excluded after the risk of bias assessment.

3.4 Data Extraction

Both reviewers extracted the following information from individual studies based on the PICO guidance and noted down in a self-made Excel table by each article's main author name, year of journal publication, study design, patient demographic, scar type, scar size and duration, any prior treatment or not, number of participants allocated to each group, type of laser used and parameters, number of participants who are lost to follow-up, treatment duration, follow-up period and response rate according to validated scar scale (e.g. VSS, POSAS, mVSS, modified Manchester quartile score (MQS), Japan Scar Workshop Scar Scale, modified Vancouver General Hospital (VGH) Burn Scar Assessment).

PICO represents P – patients, population, problem, I – intervention, C – Control or comparison, and O - outcomes. This provided a thorough and succinct summary of all the data that was gathered from the relevant research. In this systematic review, as part of our PICO, we'll use the domain listed below.

P – patients with keloid scars from any causes without considering age, gender, and ethnic origin

I – laser treatment with 585-595 nm Pulsed Dye Laser (PDL), 1064 nm Nd: YAG laser, and 10600 nm fractional CO_2 laser

C - control group or other intervention or no intervention or comparing two different laser machines

O – measurement according to VSS and other validated scar scales

3.5 Data Analysis

Data extraction and integration were carried out narratively by carefully recording, summarizing, tabulating, and integrating the study's findings using Microsoft Excel. Primary outcome measures describing overall improvement were compared according to each laser type. Results were presented descriptively since there was heterogeneity among studies. Although the primary outcome of interest was similar between all studies, there were differences in the assessment methods used. Results were discussed and summarized in the text as well as by building a comprehensive table detailing each study that was thoroughly analyzed.

Chapter 4

Research Results and Discussion

4.1 Search and Selection Results

A total of 1375 articles from 3 computerized databases were identified (Appendix A). Of these, 109 duplicates and 472 studies before the year 2010 were excluded. After title and abstract screening of the remaining articles, 100 studies were sought for full-text retrieval. Except for four studies (Kim et al., 2020; Potter et al., 2017; Potts et al., 2020; Shokrollahi, 2020) that could not be retrieved, and two ongoing trials (ChiCTR2300071347, 2023; TCTR20230304002, 2023), 94 studies were eligible for full-text review and after full-text assessment, 73 studies were excluded, and 21 studies were included in our systematic review. The selection of included and excluded studies is summarized in Figure 4.1.

4.2 Risk of Bias Assessment and Quality of Included Studies

According to OCEBM 2011 Levels of Evidence, 10 studies were Level 2 randomized controlled trials while 10 studies were Level 3 prospective comparative or retrospective analysis, and 1 study was Level 4 retrospective case series. There was large heterogeneity since the studies were different in the study population, scar location, causes of scar, and type of intervention with various laser parameter settings.

Two reviewers independently assessed ten randomized controlled trials for risk of bias using the RoB2 tool. Any discrepancies between the two reviewers were discussed to reach an agreement. A risk of bias summary figure (Figure 4.2) displays the risk of bias for each study and Figure 4.3 gives judgments about each risk of bias item presented as percentages across all included studies.

One trial was classified as having a low risk of bias, whereas the methodological quality of the other nine included trials raised some concerns. Seven studies described the randomization process and no studies included information on the allocation

process. In addition, blinding is challenging from a practical standpoint when comparing a laser treatment with other therapies, hence neither the participants nor the interventions were blinded in any of the RCTs that were reviewed. However, the results were evaluated by the blind observers.

On the other hand, 11 non-randomized controlled studies were critically appraised utilizing the Newcastle-Ottawa Scale (NOS) which rated the cohort and cross-sectional studies via the "star system" and the results given out by the two reviewers can be seen in Table 4.1 (see Appendix for detailed rating system in each three main categories).

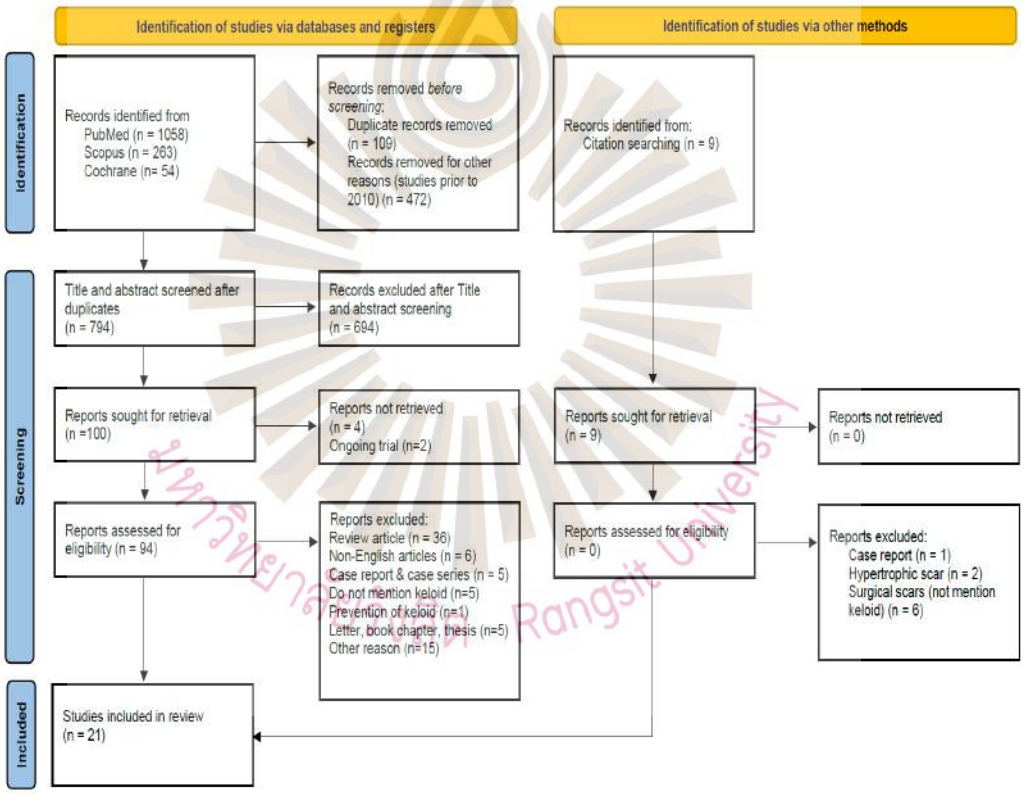

Figure 4.1 A PRISMA flow diagram describing the selection process of the studies included in this research

Source: from this study

Figure 4.2 Risk of bias summary: reviewer's judgments about risk of bias item for each included study

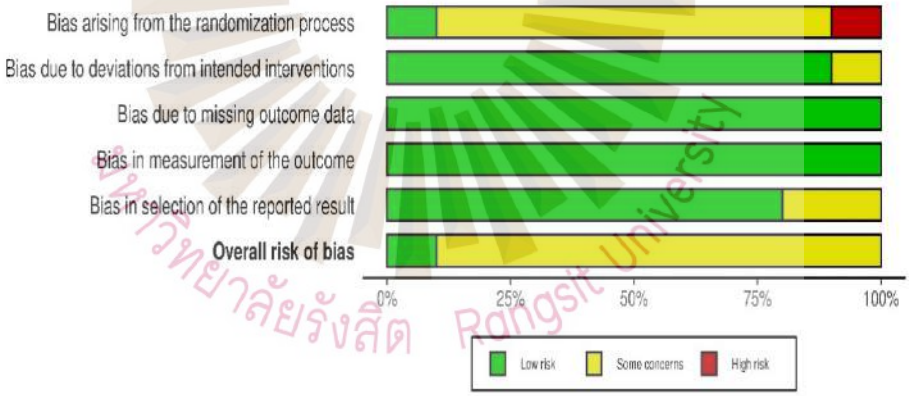

Figure 4.3 Risk of bias graph

Table 4.1 Table describing the Newcastle-Ottawa Scale for assessing the quality of cohort studies

Study	**Selection**	**Comparability**	**Outcome**	**NOS Score**	**Risk of Bias**
Cho S. (2010)	★★★	★★	★★	7/9	Good
Madan V. (2011)	★★★	★	★★★	7/9	Good
Akaishi S. (2012)	★★★	★★	★★	7/9	Good
Rossi A. (2013)	★★★	★	★★	6/9	Good
Koike S. (2014)	★★★	★★	★★★	8/9	Good
Alexander S. (2019)	★★★	★	★★	6/9	Good
Chi Xu (2020)	★★★	★	★★	6/9	Good
Khattab F.M (2020)	★★★	★★	★★★	8/9	Good
Wang J (2020)	★★★	★	★★★	7/9	Good
Alhamzawi N.K. (2021)	★★	★★	★★★	7/9	Fair
El-Hamid El-Azhary (2022)	★★★	★★	★★	7/9	Good

Good quality: 3 or 4 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome domain; Fair quality: 2 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain; Poor quality: 0 or 1 star in the selection domain OR 0 stars in the comparability domain OR 0 or 1 star in outcome/exposure domain.

4.3 Study Characteristics

4.3.1 Participants

This study included a total of 872 participants and the youngest participants were 5 years old while the oldest participants were 70 years old. Three studies did not describe the number of female and male participants however the number of female participants was slightly higher than that of men. The sample size of all the included studies was small ranging from 12-102 participants.

Twelve studies focused on keloid scars solely while nine studies had mixed hypertrophy and keloid scars in their studies. Only nine studies mentioned the Fitzpatrick skin types of the participants (skin types I-VI). Almost all the included studies mentioned exclusion criteria except two studies. The exclusion criteria were pregnancy and lactating women, participants who had treated keloid scars with any type of treatment 4 weeks to 1 year before the study, who had active viral infection and skin diseases, who had systemic isotretinoin treatment 8 months before trial, immunosuppression, history of malignancy and radiation therapy before, patients with bleeding disorders, those taking oral anticoagulants and patients with connective tissue diseases or family history of skin cancer.

4.3.2 Care setting

Seven studies were conducted in Egypt, four in China, two in India, two in Iraq, two in Japan, one in the USA, one in the UK, one in Thailand, and one in Korea. Nine studies were carried out in the outpatient clinic of the Dermatology Department in University Hospitals, two in the laser clinic of the Dermatology Department in Hospitals, two in University Hospitals, two in the Department of Burn and Plastic Surgery in Hospitals while six studies did not mention specific care settings.

4.3.3 Interventions

In this analysis, we comprised studies that compared laser therapy for hypertrophy and/or keloid scars to various therapies (including no treatment). Various

types of laser equipment and laser treatment regimes were investigated. The following interventions were performed in the included studies.

1) Fractional CO_2 laser alone vs LP-Nd: YAG laser alone vs fractional CO_2 laser followed by Nd: YAG laser (Tawfic et al., 2020)

2) Fractional CO_2 laser alone vs LP-Nd: YAG laser alone vs fractional CO_2 laser followed by Nd: YAG laser (Soliman, Etman, Abd Elhameed, Elsharaby & Tawfik, 2021)

3) Fractional CO_2 laser alone vs Intralesional Triamcinolone acetonide vs Intralesional Verapamil (Srivastava, Kumari & Singh, 2019)

4) Fractional CO_2 laser alone vs fractional CO_2 laser + Intralesional Triamcinolone acetonide vs fractional CO_2 laser followed by application of 20% Trichloroacetic acid (El-Hamid El-Azhary, Abd Al-Salam, El-Hafiz & Maghraby, 2022)

5) Fractional CO_2 laser vs no treatment (Azzam, Bassiouny, El-Hawary, El Maadawai, Sobhi & El-Mesidy, 2016)

6) Fractional CO_2 laser followed by 5-FU injection (Alhamzawi, 2021)

7) Fractional CO_2 laser followed by Intralesional Triamcinolone acetonide vs Intralesional Triamcinolone acetonide alone (Sahib, Al-Hattab, Fakhry & Atiyah, 2020)

8) Fractional CO_2 laser followed by topical Triamcinolone acetonide vs Intralesional Triamcinolone acetonide alone (Tawaranurak, Pliensiri & Tawaranurak, 2022)

9) Fractional CO_2 laser followed by Intralesional Triamcinolone acetonide vs Intralesional Triamcinolone acetonide alone (Alexander, Girisha, Sripathi, Noronha & Alva, 2019)

10) Fractional CO_2 laser followed by topical Triamcinolone acetonide (Wang et al., 2020)

11) Nd: YAG laser alone vs Nd: YAG laser + Intralesional Bleomycin (Ramadan, Saber, Salah & Samy, 2021)

12) Nd:YAG laser alone vs Nd:YAG laser + Intralesional Triamcinolone acetonide vs Intralesional Triamcinolone acetonide alone (Rossi, Lu, Frey, Kubota, Smith & Perez, 2013)

13) LP - Nd: YAG laser + topical corticosteroid (Akaishi et al., 2012)

14) LP - Nd: YAG laser alone (Koike et al., 2014)

15) 1064 nm QS Nd: YAG laser alone (Cho et al., 2010)

16) Intralesional Diprospan vs Intralesional Diprospan + 5-FU vs 1064 nm Nd: YAG laser + Intralesional Diprospan + 5 - FU (Chen et al., 2017)

17) 585 nm PDL followed by Nd: YAG (dual wavelength laser) (Xu, Ting, Teng, Long & Wang, 2021)

18) 595 nm PDL vs 1064 nm LP - Nd: YAG laser (Al-Mohamady, Ibrahim & Muhammad, 2016)

19) PDL vs PDL + Intralesional Triamcinolone acetonide (Madan, Stephanides, Rai, August & Ferguson, 2011)

20) PDL followed by Intralesional Verapamil vs Intralesional Verapamil alone (Khattab, Nasr, Khashaba & Bessar, 2020)

21) PDL alone vs no treatment (Yang et al., 2012)

4.3.4 Study Method

The course of treatment and its duration varied widely among the studies. The included trials compared two or three treatments: laser alone therapy compared with topical and intralesional injection or no treatment area serving as the control. This made comparing research results among them challenging. Furthermore, most of the trials conducted 4 treatment sessions with 4-6 weeks intervals. However, one study provided treatment for 24 weeks at 3-week intervals or until the scar became flattened (Srivastava et al., 2019). Madan and Akaishi performed an average number of 14 treatments (Akaishi et al., 2012; Madan et al., 2011). Additionally, there were differences in the follow-up period after completing the final treatment session. While some studies evaluated the scar characteristics improvement immediately after the treatment cycle, others evaluated in the longer term with follow-up visits for six months. The longest follow-up duration was 24 months by Wang et al. (Wang et al., 2020).

4.3.5 Outcome of Interventions

The evaluation of the results showed a lot of variability. While all the research had a similar primary result of interest, the assessment techniques employed varied.

Most studies used VSS as the main outcome measurement, and five studies utilized VSS, one used both VSS and POSAS, one used VSS and LSCI, one used VSS and CDU, one used VSS and MQS, one used modified VSS and one used VSS together with scar volume measurement and pain score via self-assessment using VAS (visual analog scale). Three studies utilized POSAS alone for outcome measurement while other studies used the Japan Scar Workshop Scar Scale, Manchester Quartile Scale, and modified Vancouver General Hospital Burn Scar Assessment. Rossi et al. used a quality-of-life survey and recorded a change in erythema and thickness (Rossi et al., 2013) while Sahib et al. reported an overall average improvement score including hypertrophy, texture, and color (Sahib et al., 2020). The outcomes of the research were evaluated by using parameters such as erythema, hypertrophy, hardness, itchiness, and pain/tenderness in Akaishi's study (Akaishi et al., 2012). One study reported the qualitative outcome resulting from Satisfaction Questionnaires to rate the participant's response to treatment using a scale of 0-10 (Madan et al., 2011).

Only four studies (Alhamzawi, 2021; Koike et al., 2014; Ramadan et al., 2021; Wang et al., 2020) mentioned the recurrent rate. The adverse events such as pain, hypo/hyperpigmentation, erythema, edema, discharge, telangiectasia, ulceration, skin dystrophy, lipodystrophy, purpura, and blisters were recorded in almost all studies except four studies which had no information on complications after the study.

Four studies (Al-Mohamady et al., 2016; Azzam et al., 2016; Chen et al., 2017; Wang et al., 2020) reported loss to follow-up during the follow-up period and dropped out during the study period.

4.3.6 Effects of Interventions

4.3.6.1 Pulsed Dye Laser

585 nm PDL followed by Nd: YAG laser (Dual wavelength laser) (1 study)

Outcome measurement

Xu and colleagues studied 54 keloids and the results were evaluated by VSS, and the scores were significantly decreased ($P < 0.001$) in keloids at all locations (chest,

scapula, back) after 4 sessions of treatment. Vascularity and pliability were said to play an important role in this reduction.

Blood perfusion in keloids was measured by Laser speckle contrast imaging (LSCI) and perfusion was significantly decreased after 4 sessions of treatment ($P < 0.05$). The study showed that there was a positive correlation between decreased perfusion and reduced total VSS score ($R^2 = 0.84$).

Correlation with demographic data

Regarding the anatomy, the blood perfusion and total VSS score of chest keloids were significantly greater than scapular keloids ($P < 0.05$).

Treatment-related adverse effects

There were no reported complications after the study, and it was said that all 4 sessions of treatment were well tolerated by the participants.

Recurrent rate

The recurrent rate was not reported.

595 nm PDL vs 1064 nm LP-Nd: YAG laser (1 study)

Outcome measurement

Both hypertrophic and keloid scars were included in this study and lesions were equally divided to be randomly treated with 595 nm PDL and 1064 nm LP-Nd: YAG laser for 6 treatment sessions. The outcomes were measured by VSS and a significant improvement in the total score of both laser modalities was seen ($P < 0.001$). However, there were non-significant differences in total VSS score between PDL and Nd: YAG laser after the final therapy ($P = 0.74$). Al-Mohamaday et al. reported that Nd: YAG had better results with hypertrophic scars while PDL had better outcomes with keloid scars.

There was a significant improvement in scar erythema, height, and pliability. It was reported that the Nd: YAG laser had experienced more improvement in pliability when compared to PDL.

Correlation with demographic data

A strong negative correlation was seen between the total improvement of scar score and scar age as well as between skin type and total improvement of score.

Treatment-related adverse effects

Mild to moderate pain at treatment sites was reported especially with Nd: YAG laser. Purpura (35%) and hyperpigmentation (10%) were noted after PDL treatment and bullae were seen in 10% of participants with Nd: YAG laser treatment.

Recurrent rate

The authors did not report a recurrent rate.

595 nm PDL vs 595 nm PDL + Intralesional Triamcinolone acetonide (1 study)

Outcome measurement

Madan and associates conducted a retrospective case series of 99 patients with a total of 755 keloids and their response to treatment was asked by satisfaction questionnaire to rate from 0 to 10 (0 indicating no improvement and 10 indicating complete clearance) and to address the improvement of symptoms including redness, thickness, discomfort, and itching as well as the side effects.

The record showed that 76% of the patients saw a moderate to excellent result after combination therapy (PDL + IL Corticosteroid). The average response to treatment was 8 in females and 7 in males.

According to the satisfaction survey, the most improvement was seen in the thickness of keloids (70%) followed by improvement in pruritus (64%) and redness (50%). The least improvement was discomfort accounting for 13%.

Treatment-related adverse effects

Redness, discomfort, and pruritus were reported as side effects after the treatment.

Recurrent rate

The recurrent rate was not mentioned in this retrospective study.

595 nm PDL and Intralesional Verapamil vs Intralesional Verapamil (1 study)

Outcome measurement

Forty patients with 56 keloids were included in this research and measurement of outcomes was done by utilizing VSS, and modified Manchester quartile score (MQS) for evaluation of improvement in overall appearance, dyschromia, the degree of hypertrophy, and texture. Patients were also asked to rate the level of improvement on a scale of 1 - 4 (1 – none, 2 – fair, 3 – good and 4 – very good).

Combination therapy demonstrated significant improvement in vascularity ($P < 0.001$). Both combination therapy and monotherapy showed significant reduction in height ($P = 0.003$) and pliability ($P = 0.025$). Neither combination nor monotherapy had the desired change in pigmentation.

According to the modified MQS, an improvement of more than 50% was seen in overall appearance, degree of hypertrophy, and dyschromia. The least improvement was seen in texture. Compared to the monotherapy group, the combination treatment group had the highest level of patient satisfaction, and this difference was statistically significant ($P = 0.003$).

Treatment-related adverse effects

Adverse events were more common in the group receiving monotherapy which included an increase in size, pain, hyperpigmentation, and depigmentation.

Recurrent rate

The research authors did not report on recurrent rates.

PDL alone vs no treatment (1 study)

Outcome measurement

Yang et al.(2012) studied 26 patients with keloids treated with 595 nm PDL which was compared to the untreated site after 3 sessions of irradiation. The results were assessed by VSS. It was reported that the VSS score significantly decreased ($P < 0.05$) by 20.85 ± 12.33% on average. The principal factors influencing the decline in VSS score were improvement of scar texture, relief of symptoms, and decrease in redness.

In addition to the VSS score, the biopsy was conducted on both treated and untreated keloids to investigate connective tissue growth factor mRNA expression (CTGF mRNA). There was a significant downregulation in CTGF mRNA in 80.77% of cases compared to the baseline ($P < 0.05$).

Correlation with demographic data

It was shown that there was a negative correlation between CTGF mRNA and the age of the patient indicating that the downregulation of CTGF mRNA was more pronounced in older patients. On the other hand, the duration of keloid did not appear to be significantly correlated with CTGF mRNA expression.

Treatment-related adverse effects

The following side effects were reported after laser therapy which included blister (22.22%) and hyperpigmentation (48.15%).

Recurrent rate

No information on recurrent rates in this research.

4.3.6.2 1064 nm Nd: YAG Laser

Nd: YAG laser alone vs Nd: YAG laser + Intralesional Bleomycin (1 study)

Outcome measurement

This study included 40 participants with hypertrophic scars and keloids divided into two groups; one group handled by long pulsed Nd: YAG laser and another group treated with a combination of long pulsed Nd: YAG laser and IL bleomycin every 4 weeks for a total of 5 sessions. Treatment responses were evaluated by using modified VSS.

In combination therapy, there was a highly significant difference between pre- and post-treatment vascularity, pigmentation, pliability, height, and itchiness except for pain. In terms of Nd: YAG laser monotherapy, there was no significant change in pain or pigmentation, but there was a substantial difference in vascularity, pliability, height, and itching before and after the therapy. Furthermore, the median value of the modified VSS total score varied significantly between the before and after therapy periods (P = 0.043).

Treatment-related adverse effects

The complications such as hyperpigmentation and ulceration were slightly higher in combined therapy and hypopigmentation was somewhat more prevalent in the monotherapy group.

Recurrent rate

Following 6 months, the recurrence rate with monotherapy was 45 percent against 15 percent with combination treatment.

Nd: YAG laser alone vs Nd: YAG laser + Intralesional Triamcinolone acetonide vs Intralesional Triamcinolone acetonide alone (1 study)

Outcome measurement

The treatment efficacy of 44 patients with keloids was retrospectively analyzed and the outcome was measured clinically by evaluating a change in the erythema and the thickness of the keloids was recorded. A grading system was utilized to measure the improvement; mild (25-50% reduction in erythema and thickness), moderate (50-75% reduction in erythema and thickness) and marked (>75% reduction in erythema and

thickness). In addition, a survey assessing changes in quality of life was handed out to patients.

The Nd: YAG laser and intralesional triamcinolone acetonide combination group had the greatest outcomes, with a significant decrease in thickness and erythema observed in every patient. There were mixed results for the patients undergoing just laser treatment, however, most of them reported a moderate reduction in thickness and erythema. The control group (IL Triamcinolone acetonide alone), on the other hand, saw little to no reduction. The keloid improvement across the treatment groups was described as statistically significant ($P < 0.0001$).

All patients in the combined treatment group and the laser-alone therapy group reported a higher quality of life than those in the control group after the treatment.

Treatment-related adverse effects

The study found that the side effects of laser therapy were less severe than the pain from intralesional injections. Treatment-related side effects were limited to transient erythema following therapy and transient pain during treatment. Remaining post-inflammatory hyper- or hypopigmentation, scarring, or further keloid formation were not seen.

Recurrent rate

This study did not provide information on the recurrence rate.

LP - ND: YAG laser + Topical corticosteroid (1 study)

Outcome measurement

Akaishi et al. (2012) examined 22 patients with keloids and hypertrophic scars using long pulsed Nd: YAG laser in non-contact mode and giving corticosteroid ointment for 2-3 days after the treatment to minimize the bullae formation after irradiation. The response to the therapy was evaluated by assessing the following 5 parameters: erythema, hypertrophy, hardness, itching, and pain or tenderness. A 4 -

point grading system, ranging from 0 to 3, was used for scoring (0 = absent, 1 = mild, 2 = moderate, 3 = severe).

There were significant improvements in all parameters ($P < 0.01$ for all) after an average of 14.05 treatment sessions. The itching was remarkably improved after irradiation. While there was some improvement in the hypertrophic scars, it was not statistically significant ($P = 0.058$), but the laser treatment considerably improved the keloids ($P < 0.01$).

Correlation with demographic data

After laser therapy, the average total score of the low-tension site scar group significantly improved (P at least < 0.05).

Treatment-related adverse effects

There was no information on treatment adverse events.

Recurrent rate

There was no information on the recurrence rate in this investigation.

LP - Nd: YAG laser alone (1 study)

Outcome measurement

This retrospective cohort research consisted of 102 patients with 64 keloids and 38 hypertrophic scars treated with 1064 nm Nd: YAG laser in contact mode every 3 - 4 weeks for 1 year. The scars were assessed utilizing the 2011 Japan Scar Workshop Scar Scale which included 6 variables: induration, elevation, scar redness, erythema around the scars, spontaneous and pressing pain, and itch. The score was based on a 4-point scale ranging from 0 to 3 (0 = none, 1 = weak, 2 = mild, 3 = strong) thus the maximum score was 18 points.

After one year of therapy, the average overall Japan scar workshop scores of keloids and hypertrophic scars considerably decreased from their pre-treatment levels (all $P < 0.05$). Most of the hypertrophic scars had transformed into almost mature scars

since the average post-treatment scores for all hypertrophic scar groups were less than two points. All keloid groups, however, had average post-treatment scores greater than two points. Moreover, there were 3 out of 34 anterior chest keloids that did not respond to the treatment at all.

The authors concluded that hypertrophic scars reacted noticeably better to 1064 nm Nd: YAG laser therapy compared to keloids.

Correlation with demographic data

Less response to therapy was observed in the anterior chest keloids. In terms of the anatomic area of the scars, no significant difference between the afflicted body areas was seen ($P > 0.05$).

Treatment-related adverse effects

No adverse events were mentioned in this cohort.

Recurrent rate

The assessment of recurrence was conducted six months following the end of therapy, at which point 25% of scapula keloids, 52.9 % of anterior chest keloids, 35.7 % of upper arm keloids, and 4% of total abdominal hypertrophic scars recurred.

1064 nm QS Nd: YAG laser alone (1 study)

Outcome measurement

In this retrospective investigation, hypertrophic scars, and keloids in 21 anatomic locations of 12 Korean patients were treated with low influence 1064 nm Q-switched Nd: YAG laser for several sessions at 1 - 2 weeks intervals. The mean number of treatment sessions was 7.8 (range 5 - 10) which was determined according to the treatment response, patient satisfaction, and demand.

Modified Vancouver General Hospital Burn Scar Assessment (VGH) comprising four parameters: lesion pigmentation (rating 0 - 2), vascularity (0 - 3), pliability (0 - 5), and height (0 - 3) was used to evaluate the final score. Patients were

asked to rate their overall level of satisfaction using the following scale three months after the last treatment: very satisfied, satisfied, slightly satisfied, and dissatisfied.

The sum of the scores for each component, or the VGH score, dropped from 8 (range 6 - 12) to 6 (range 3 - 8) ($P < 0.0001$). Pliability changed the greatest from baseline, accounting for 34.4 percent. Vascularity and pigmentation changed by 33.3 and 32.4 percent, respectively. With an average improvement of 22.9 percent, height showed the least gain among the assessed parameters.

According to the level of patient satisfaction, 11 out of 21 keloids and hypertrophic scars (52.4%) had a very satisfied or satisfied response, six had a slightly satisfied response, and four had an unsatisfied response. According to the regression model, which included variables made up of the VGH score components, patient satisfaction was shown to be impacted by the percent change in pigmentation and vascularity but not by pliability or height.

Correlation with demographic data

The etiology, locations, and prior treatment methods of keloids and hypertrophic scars did not substantially affect changes in any of the individual component scores or the VGH score.

Treatment-related adverse effects

There were no obvious side effects, such as the lesion getting worse or developing dyschromia after therapy. Two minor adverse effects that were noted were slight erythema following treatment and a mild prickling sensation during treatment, both of which subsided in a few hours.

Recurrent rate

No details are available on the recurrence rate.

Intralesional Diprospan vs Intralesional Diprospan + 5-FU vs 1064 nm Nd: YAG laser + Intralesional Diprospan + 5-FU (1 study)

Outcome measurement

In this three-month single-center clinical trial, 69 patients with keloids were randomly divided into 3 groups, and each group was treated with IL corticosteroid, a combination of 5-FU and corticosteroid injection, and irradiation with 1064 nm Nd: YAG laser followed by injection of 5-FU and corticosteroid respectively with one-month intervals for 3 sessions. Clinical response was assessed based on the patient's self-report on a 5-point scale that is no improvement, poor improvement (< 25%), fair improvement (26 - 50%), good improvement (51 - 75%), and excellent improvement (76 - 100%). On the other hand, an observer's overall evaluation was based on the clinical indicators of pliability, pruritus, and erythema.

According to patient self-assessment and observer assessment, improvements were evaluated lowest in the Diprospan group and greatest in the Diprospan + 5FU + Nd: YAG group. By the time the trial ended, the Diprospan + 5-FU + Nd: YAG group had much less erythema and toughness than the other groups, and their reduction in itching was also significantly larger ($P < 0.05$ for all indexes). The acceptable responses (good to excellent improvements) reported by blinded observers were as follows: 12% in the Diprospan group, 48% in the Diprospan + 5-FU group, and 69% in the Diprospan + 5-FU + Nd: YAG group. Based on all the data, the best effective treatment for keloid scars was a combination of Diprospan, 5FU, and Nd: YAG laser.

Treatment-related adverse effects

Thirty-six percent of individuals in the Diprospan group had some degree of telangiectasia and skin atrophy. The Nd: YAG laser-treated site in the Diprospan + 5-FU + Nd: YAG group developed a purpuric color for seven to ten days. In either the Diprospan + 5-FU or the Diprospan + 5-FU + Nd: YAG group, there were no unfavorable textural or pigmentary changes. Additionally, no erosions or ulcers were noticed.

Recurrent rate

The recurrence rate was not described by the authors.

4.3.6.3 10600 nm Fractional Carbon Dioxide Laser

Fractional CO_2 laser alone vs LP - Nd: YAG laser alone vs Fractional CO_2 laser followed by Nd: YAG laser (2 studies)

Tawfic et al.(2020) compared the efficacy of fractional CO_2 laser, long pulsed Nd: YAG laser, and their combination in 30 patients with hypertrophic and keloid scars, three scars in each patient were randomly assigned to the treatment. On the other hand, Soliman et al.(2021) divided 45 patients into 3 equal groups and each group received fractional CO_2 laser only, Nd: YAG laser only, and a combination of both lasers respectively. The treatment duration for both studies was the same, with 4 treatment sessions at 4 - 6 weeks intervals.

Outcome measurement

In Tawfic's research, the results were measured using both VSS and POSAS, while Soliman's study just employed POSAS. Tawfic et al. stated that both VSS and POSAS showed significant improvement following treatment with the three used modalities ($P = 0.0001$), with pliability showing the greatest improvement. However, there was no significant difference when comparing the three treatment modalities, VSS ($P = 0.682$) and POSAS ($P = 0.229$). The authors reported that fractional CO_2 laser yields better improvement in hypertrophic scars, while in keloids both fractional CO_2 and Nd: YAG lasers achieve comparable improvement.

When Soliman assessed the results using POSAS, the combination group had the greatest clinical improvement, followed by the fractional CO_2 group, while the least improvement was seen in the Nd: YAG group. Regarding patient satisfaction, there was a statistically significant variation across the various laser treatments. The combined group of patients and the fractional CO_2 laser group reported higher levels of satisfaction, 93.3 and 86.7 percent, respectively, compared to just 40 percent in the Nd: YAG group. The results of the study demonstrated that fractional CO_2 and Nd: YAG

lasers work best together to control keloids, with fractional CO_2 being more effective than Nd: YAG and Nd: YAG being the least effective.

Correlation with demographic data

In Tawfic's study, all treatment modalities showed non-significant correlations between scar improvement and scar duration, scar site, and patient age, except for scar duration, which was significantly correlated with the VSS score of Nd: YAG laser-only therapy.

Treatment-related adverse effects

Tawfic (2020) mentioned that the combination of two lasers in the same session did not add significant additional benefits and the side effects profile was higher. Hyperpigmentation was reported especially when treatment included fractional CO_2. Hypopigmentation occurred in three patients who received a combination of fractional CO_2 and Nd: YAG lasers. All patients reported mild-to-moderate pain during and after Nd: YAG laser therapy; however, severe pain was reported by 10 patients and mild-to-moderate pain by 20 patients in fractional CO_2 alone and combined laser treatment group. Erythema, edema, and discharge following ablative CO_2 laser treatment were noted by all patients.

Soliman (2021) stated that all groups tolerated the adverse effects which were mostly mild. Fractional CO_2 laser therapy was associated with higher rates of erythema, hyperpigmentation, discomfort, and burning sensation; in contrast, hypopigmentation was more prevalent in the combined laser group and Nd: YAG laser group. With fractional CO_2 laser, other mild side effects such as milia, dermatitis, and itching were seen.

Recurrent rate

There had been no documented recurrence in both Tawfic and Soliman studies.

Fractional CO_2 laser alone vs Intralesional Triamcinolone acetonide vs Intralesional Verapamil (1 study)

Outcome measurement

In a randomized parallel-group trial, three groups of sixty patients were assigned at random to the study. The first group had fractional CO_2 laser treatment; the second group received triamcinolone acetonide and the third group received intralesional verapamil every three weeks for six months. The results were assessed using the Vancouver Scar Scale score (VSS).

All three groups had a decrease in scar height, vascularity, and pliability. Nevertheless, none of the three modalities was able to eliminate pigmentation. Triamcinolone acetonide elicited the fastest reaction, followed by verapamil and laser; nevertheless, there was no statistically significant difference in the rate of pigmentation with any of the three treatments. There was a reduction in pain and pruritus in all three groups and lesser injection site pain with verapamil.

Treatment-related adverse effects

The laser and triamcinolone acetonide groups experienced minor side effects. There were no negative effects observed in the verapamil group. Pain during injection was noted in the triamcinolone acetonide group, and the laser group showed charring.

Recurrent rate

Owing to limited follow-up, it is impossible to pinpoint the precise recurrence estimate.

Fractional CO_2 laser alone vs Fractional CO_2 laser + Intralesional Triamcinolone acetonide vs Fractional CO_2 laser followed by application of 20% Trichloroacetic acid (1 study)

Outcome measurement

Forty-five participants with keloid scars at different sites of the body were classified into 3 groups and treated by fractional CO_2 laser only, fractional CO_2 laser followed by triamcinolone acetonide, or trichloroacetic acid application, respectively for 4 sessions 4 weeks apart. Evaluation of the keloid was done with Vancouver Scar Scale (VSS) and Color Doppler Ultrasound (CDU) before and after treatment, as well as patient satisfaction by patient satisfaction self-assessment (score from 0 to 4; not satisfied 0%, mildly satisfied < 25%, moderately satisfied 25 - 50%, very good satisfied 50 - 75% or excellent satisfied > 75%).

The results showed a statistically significant reduction in VSS of pre- and post-treatment in each group with $P < 0.01$. There was a high statistically significant reduction in VSS among the 3 groups ($P < 0.001$); the reduction was more in the laser combined with intralesional corticosteroid group than in the laser alone group and a slight reduction was seen in laser therapy followed by topical 20% trichloroacetic acid.

Following treatment, all three groups showed statistically significant reductions in the keloid thickness as evaluated by CDU; laser therapy alone showed the largest radiological decrease (-1.55 ± 5.22), followed by laser combined with intralesional corticosteroid group (-1.24 ± 2.13), and laser therapy followed by topical 20% trichloroacetic acid group showed the least (-0.12 ± 0.15). There was no statistically significant association seen between the radiological and clinical responses.

Patient satisfaction grades 3 and 4 were the highest among the laser-only group and combined laser and intralesional corticosteroid group, while grades 1 and 0 of the score were the highest among patients of the combined laser and topical trichloroacetic acid group. The present investigation did not find a statistically significant correlation between the patient satisfaction self-assessment score and the clinical response as determined by VSS.

Correlation with demographic data

Clinical or radiological responses did not show a statistically significant correlation with the patient's sex, skin phototype, keloid origin, place, size, multiplicity, or history of therapy. Nonetheless, the non-bony locations showed superior clinical

improvement, with a mean VSS decrease of -3.36 (± 1.39) compared to -2.77 (± 1.69) at the bony sites.

Treatment-related adverse effects

Twenty of the total patients experienced no side effects, while the remaining 25 patients experienced discomfort, itching, ulceration, hypopigmentation, and hyperpigmentation. Regarding side effects, the data revealed a statistically significant difference ($P < 0.05$) between the three groups. Patients in laser alone and laser combined with intralesional corticosteroid group experienced mild side effects like pain and itching, while patients in laser therapy followed by topical 20% trichloroacetic acid group experienced severe side effects like ulceration, hypopigmentation, and hyperpigmentation in addition to pain and itching.

Recurrent rate

The researchers did not notice any recurrence among studied cases which may be due to the short period of follow-up (8 weeks).

Fractional CO_2 laser vs No treatment (1 study)

Outcome measurement

Thirty patients (18 keloids and 12 hypertrophic scars) had four sessions of fractional CO_2 laser treatment on one randomly selected half of the scar, while the other half was left as a control. Vancouver scar score (VSS) was evaluated before and 1, 3, and 6 months after the last laser session by a blinded observer. Nineteen patients (12 keloids and 7 hypertrophic scars) finished the six-month follow-up period; eight patients dropped after the second and third laser treatments, two patients did not show up for the follow-up in the third month, and one patient did not return for the follow-up in the sixth month. Patient satisfaction was asked after completing all four sessions and rated as excellent (> 75% improvement), good (50 - 75% improvement), moderate (25 - 50% improvement) and poor (< 25% improvement).

There was a significant reduction in VSS score in the treated areas compared to untreated areas after 3 and 6 months in both keloid and hypertrophic scars. This

difference was mostly contributed by improved pliability of the scar in the keloid group and both pliability and pigmentation in the hypertrophic scar group. Pain and pruritus were reported to be relieved after the treatment.

Out of the twelve keloid patients who finished the research, 6 were poorly satisfied, 3 expressed good and 3 had moderate satisfaction. Of the seven patients in the hypertrophic group, two considered the therapy's result to be excellent, one good, two moderate, and two poorly satisfied.

Correlation with demographic data

The percentage of reduction in VSS score in both the keloid and hypertrophic scar groups did not significantly correlate with the patient's age, scar duration, or the site of lesion (head, neck, and upper limb vs other sites).

Treatment-related adverse effects

This research did not evaluate this data.

Recurrent rate

No documented recurring rate was found.

Fractional CO_2 laser followed by 5-FU injection (1 study)

Outcome measurement

A total of six sittings of fractional CO_2 laser therapy were followed by injections of 5-FU for 24 patients with 44 keloids in this prospective open-label trial. Using the Vancouver Scar Scale (VSS), the clinical response in terms of height, pliability, vascularity, and pigmentation was the main outcome assessed.

A significant reduction was observed in the VSS in terms of pliability and height after three treatment sessions. The mean VSS decreased by 65%, from 8.45 ± SD 0.93 at the baseline to 3 ± SD 1.8 one month following the final treatment ($P < 0.05$). Pliability was the most noticeable difference for every patient. In addition, height was decreased by 83%, vascularity by 20.8%, and pigmentation by 16.6% of the patients.

Most patients responded to therapy satisfactorily, with 57.8% attaining an excellent result. Patients who had experienced itching before treatment no longer experienced it.

Correlation with demographic data

There was a significant association seen between the variations in VSS and the duration of keloids; 13 out of 19 patients who showed a satisfactory response had keloids that lasted less than three years ($P < 0.05$). Regarding the patient's age, no discernible association was discovered.

Treatment-related adverse effects

Adverse reactions included pain, redness, and edema which were transient, lasting no more than a week. Post-inflammatory hyperpigmentation was observed in four patients and skin erosion in two.

Recurrent rate

Recurrences after a follow-up of 1 year were reported in 21% of the patients who responded well.

Fractional CO_2 laser followed by Intralesional Triamcinolone acetonide vs Intralesional Triamcinolone acetonide alone (2 studies)

Alexander et al. (2019) divided 50 patients with keloids and hypertrophic scars into two groups, each group receiving laser therapy followed by intralesional corticosteroid injection and intralesional corticosteroid injections alone respectively with a minimum of four sessions. On the other hand, Sahib et al. studied 22 patients with keloids and hypertrophic scars by dividing them into two groups. A combination of laser and intralesional corticosteroid therapy was compared to injection corticosteroid alone with a total course of 4 months at one-month intervals.

Outcome measurement

According to Alexander (2019), the improvement in overall appearance, dyschromia, degree of hypertrophy, and texture were evaluated with a modified Manchester quartile score (MQS). On a scale of 1 – 4, the patients were asked to rank their degree of improvement: 1 = none, 2 = fair, 3 = good, and 4 = very good.

After comparing the groups' post-treatment keloid and hypertrophic scars measurements, a statistically significant decrease in length (P = 0.025) and height (P = 0.003) was found. There was no discernible improvement in breadth (P = 0.902). Every parameter of the modified MQS was compared between the laser and corticosteroid injection group, and the intralesional corticosteroid monotherapy group in each session, and the results indicated statistically significant improvement in the combination group compared to the monotherapy group in all four parameters.

The results showed that the combined treatment group had higher patient satisfaction than the monotherapy group, and that difference was statistically significant (P = 0.003). There was a significant positive correlation found between modified MQS parameters and patient satisfaction scores.

Sahib et al.(2020) utilized the 4-point scale to record the degree of improvement: improvement for < 25% was 0, 25 - 50% was 1, 50 - 75% was 2 and > 75% was 3. They considered the degree of improvement of < 25% as a mild response, 25 - 75% as a moderate response, and > 75% as a good response. For the combination group, the average general score was 2.8, which corresponds to a range of 2 to 3; moreover, 7 out of 11 patients had the highest average improvement score of 3. In the monotherapy group, the greatest average total improvement score was 2.5 which was seen in 2 of 11 patients.

Correlation with demographic data

Alexander found that all five lesions that regrow after the treatment were on the chest and were observed in men, given that the chest is a high-tension region with high mobility.

Treatment-related adverse effects

In Alexander's study, the following adverse effects were reported: increase in size, pain, hyperpigmentation, and depigmentation which were more common in the combined therapy group than corticosteroid injection alone group, but the difference was not statistically significant (P = 0.0653). Regrowth of the lesion was the most frequent side effect seen, occurring in 8.9% of 5 lesions; this percentage was somewhat greater in the laser combined with intralesional corticosteroid group (3/5) than in the intralesional corticosteroid alone group (2/5).

Sahib's experiment revealed no untoward side effects except for mild pain and temporary erythema in a few participants right after treatment.

Recurrent rate

There was no recurrent rate data in either of the trials.

Fractional CO_2 laser followed by Topical Triamcinolone acetonide (1 study)

Outcome measurement

In this prospective research, eight therapy sessions with ultrapulse fractional carbon dioxide laser (UFCL) and topical triamcinolone acetonide (40 mg/mL) were administered to forty-one people with refractory keloids at four-week intervals. After applying topical triamcinolone to the whole region, it was covered for four hours with a clear film dressing. Patients were monitored for 24 months following the end of therapy. The Patient and Observer Scar Assessment Scale (POSAS) was used to assess how combination treatment affected scar pliability, thickness, alleviation, vascularization, surface area, pain, and itching.

After receiving the whole course of therapy, 38 patients finished the full 24-month follow-up, whereas 3 patients were lost to follow-up at the 6^{th} and 12^{th} month. The mean keloid POSAS scores showed a decreasing trend in subsequent times. Between the baseline and 24 months following the commencement of therapy, all POSAS components considerably improved ($P < 0.05$). Every component of the patient and observer scores decreased, with the most notable drops occurring in the areas of pain, itching, thickness, stiffness, pliability, color, and relief.

No improvement was seen in two of thirty-eight patients and their POSAS scores remained unchanged at any follow-up visit between baseline and 24 months.

Long-term follow-up data show that topical triamcinolone and ultra pulse fractional CO_2 laser combination keloid therapy have a low recurrence rate, a long-term stable course of treatment, and an overall considerable improvement.

Treatment-related adverse effects

Four individuals had hyperpigmentation, and one patient experienced a telangiectasia problem.

Recurrent rate

Out of all the patients, 4 patients experienced recurrence and the POSAS scores of those patients exhibited a noteworthy rising trend at 6, 12, and 24 months following the completion of their therapy. Also, infection was the root cause of all recurring instances.

Fractional CO_2 laser followed by topical Triamcinolone acetonide vs Intralesional Triamcinolone acetonide alone (1 study)

Outcome measurement

Tawaranurak et al. (2022) also conducted a randomized controlled trial (RCT) including 22 keloid patients who were allocated randomly to two groups: laser followed by topical corticosteroid and injection corticosteroid alone, respectively, at 4-week intervals until the keloids were resolved. Following the laser treatment, 0.1% triamcinolone acetonide cream was advised to be used twice daily for one week.

Throughout each month of the one-year visit, the scar volume and score on the Vancouver Scar Scale (VSS) were assessed. The visual analog scale (VAS) was used to self-assess the pain score.

The mean scar volume was significantly decreased in both the combined treatment group and monotherapy group ($P < 0.001$ in both groups). Scar volume

significantly decreased after two months with injecting corticosteroid alone and four months with laser coupled with topical triamcinolone acetonide. Upon completion of a 1-year treatment, the monotherapy group saw a higher percentage of scar volume change than the combined group (86.5 percent vs. 59.1 percent, P = 0.16). In both groups, there was a marked reduction in the mean VSS score (P < 0.001). Nevertheless, at the 1-year treatment interval, no statistically significant difference was seen between the groups (P = 1.000). When comparing the combination group to the monotherapy group, the mean VAS score tended to be higher in the monotherapy group (P = 0.178). Nevertheless, pain ratings were reported to have greatly decreased in both groups one minute following the treatment, with no significant difference seen between the two groups.

Treatment-related adverse effects

Six of the eleven patients in the corticosteroid injection alone group had adverse effects, including two cases of lipodystrophy and four cases of hypopigmentation. Regarding patients from the combined treatment group, no adverse effects were noted.

Recurrent rate

In patients receiving combination therapy, the percentage of entirely cured keloids was 63.6%, whereas in those receiving monotherapy, it was 72.7%. Recurrence was more common in the intralesional corticosteroid injection group (18.2%) than in the laser followed by the topical triamcinolone acetonide group (9.1%).

4.4 Discussion

Keloids are pathological scars caused by the excessive proliferation of fibroblasts and are more common in darker skin types. While there are several effective treatment options for keloids, the most popular and first-line approach remains injectable corticosteroid therapy. However, the application of laser treatment in scar therapy is growing due to advancements in laser technology and its best results in treating keloids. Numerous experiments were conducted to assess the effectiveness of

combining intralesional corticosteroid therapy with laser therapy in comparison to either injection or laser therapy alone.

This review is based on ten randomized clinical trials and eleven non-randomized studies with 872 participants. All trials included in this analysis evaluated the efficacy of 585-595 nm pulsed dye laser, 1064 nm Nd: YAG laser, and 10600 nm fractional CO_2 laser in combination therapy or mono laser therapy. In this systematic review, triamcinolone acetonide (TAC), verapamil, 5-FU, bleomycin, and 20% trichloroacetic acid were used in combination therapy. For keloid management, the most popular combination was intralesional steroid plus laser since glucocorticoid can cause fibroblasts to undergo apoptosis thereby reducing the quantity of fibroblasts. Concurrently, TGF synthesis was suppressed, and collagen production was decreased. This also clarifies why laser combination therapy is more effective than laser treatment alone since most laser combination therapies employ several different mechanisms whose results are attributable to superposition (Alster, 2003; Asilian et al., 2006).

In this review, five studies were obtained for PDL that compared laser treatment with no treatment (Yang et al., 2012), PDL laser treatment compared with Nd: YAG laser treatment (Al-Mohamady et al., 2016), and PDL plus intralesional treatment compared with intralesional alone or PDL laser alone treatment (Khattab et al., 2020; Madan et al., 2011) and PDL combined with ND: YAG laser treatment (Xu et al., 2021). Other types of laser, such as 1064 nm Nd: YAG laser (Akaishi et al., 2012; Chen et al., 2017; Ramadan et al., 2021; Rossi et al., 2013) and fractional CO_2 laser (Alexander et al., 2019; Alhamzawi, 2021; El-Hamid El-Azhary et al., 2022; Sahib et al., 2020; Soliman et al., 2021; Srivastava et al., 2019; Tawaranurak et al., 2022; Tawfic et al., 2020; Wang et al., 2020), were also compared with other intralesional treatments and no treatment. Studying the pre-and post-treatment effectiveness of each laser was also included in this review (Azzam et al., 2016; Cho et al., 2010; Koike et al., 2014).

The primary descriptive markers of the effectiveness of laser combination therapy and laser alone therapy are subjective indicators, objective indicators, and adverse responses. Although all the studies assessed scars, they utilized different scales such as the Vancouver Scar Scale (VSS), Patient and observer scar assessment scale

(POSAS), modified Vancouver Scar Scale (mVSS), modified Manchester quartile score (MQS), Japan Scar Workshop Scar Scale, modified Vancouver General Hospital (VGH) Burn Scar Assessment, and clinical improvement scales.

The VSS score scale is an index that evaluates changes in keloids, including pigmentation, pliability, height, and vascularity. This review suggests that the improvement rate in the total VSS score of all three types of laser therapy combined with other treatments was larger than that of laser-only treatment or injections and topical monotherapy. All three lasers improved the scar characteristics, particularly vascularity and pliability. The improvement rate in scar vascularity was greater in PDL than that of the other two laser types. The pliability was the most prominent category to improve with fractional CO_2 laser. Nd: YAG laser required multiple treatment sessions (7-14 sessions) to achieve the improvement in scar characteristics whereas PDL and fractional CO_2 laser required only 4-6 sessions. Two studies reported that Nd: YAG laser was said to be better in hypertrophic scars than keloids (Al Mohamady et al., 2016, Koike et al., 2014), contrasting to Akaishi, who said improving keloids was better than hypertrophic scars (Akaishi et al., 2012).

In terms of subjective evaluation of such issues as pain, itching, and satisfaction, the combination treatment showed that pain is the least improvement parameter where laser alone and other monotherapy (intralesional corticosteroid or intralesional verapamil) had a prominent reduction in pain and itchiness level than the laser combined treatment. Most patients were satisfied with both combination treatment and laser alone therapy while injection treatment alone showed poor satisfaction. It was mentioned that most of the patients' satisfaction was influenced by pigmentation and vascularity (Cho et al., 2010).

An important endpoint to evaluate was subjective scar assessment due to the possible psychological impact of hypertrophic and keloid scars. Unfortunately, the subjective evaluation of scars was not examined in all included research. It is to be hoped that upcoming research will utilize a standard scar assessment scale such as the POSAS in their outcome evaluation. Although complications were reported by authors, adverse events were not outcomes of interest in any of the included trials. In this

systematic review, the incidence of adverse reactions reported was mainly from the laser combination group rather than the monotherapy group. The included studies stated that most of the side effects were tolerable and transient which subsided after a week. Fractional CO_2 laser therapy was associated with higher rates of erythema, hyperpigmentation, discomfort, and burning sensation where hypopigmentation and pain were seen in the Nd: YAG group. Purpura occurred as the main complication in the PDL group. Tawfic mentioned that the combination of two lasers in the same session did not add significant additional benefit and the side effects profile was higher.

Regarding the recurrent rate, only four studies of Nd: YAG laser and fractional CO_2 laser treatment (Alhamzawi, 2021; Koike et al., 2014; Ramadan et al., 2021; Wang et al., 2020) reported the scar recurrence during the follow-up period, which is a clinically important outcome, and a prevalent condition. Alexander stated all lesions that regrew were found on the chest which is a high-tension and high-mobility area (Alexander et al., 2019). Wang J reported that after 24 months of follow-up, topical triamcinolone acetonide and ultra pulse fractional CO_2 laser combination keloid therapy have a low recurrence rate and long-term stable course of treatment (Wang et al., 2020). However, different follow-up times and various scar assessment scales may have contributed to the vast variation in results regarding treatment responsiveness. The follow-up times were short for all trials and varied between 0 and 6 months except for Wang et al. which took place for 24 months. Therefore, longer follow-up periods and bigger sample sizes are required to identify any possible variations in clinical outcomes and risks.

Even though this review covers the effectiveness of laser therapy for keloid treatment in detail, there are several research limitations to consider. Initially, this review's high level of evidence findings was not possible since no level I research was included. Secondly, there was great heterogeneity since the laser parameters adopted by the same treatment combinations were not the same across the included studies, as well as the fluence and pulse duration of each laser type were different. Therefore, a statistical meta-analysis comparing treatment modalities was not possible.

Nevertheless, bias is a major limitation of the findings from these studies since most of them simply used single blinding of assessors. One of the ten included trials had one domain which was rated high risk of bias. Furthermore, the eight trials had some concerns and only one trial had a low risk of bias in all domains. Unfortunately, certain information, particularly the missing outcome data of participants who had lost to follow-up was absent and could not be acquired from the study's authors. There was a total of 24 patients in this review who did not come back during the follow-up period. Furthermore, in some cases, data were also insufficiently reported or reported in ways that did not allow extraction and further analysis. As a result, none of the existing research had excellent methodology, and until high-quality trials are published, the real effectiveness of laser treatment may remain unclear.

Regardless of language or publication status, we included all pertinent studies in our review searches by searching the most significant databases, clinical trials, connections with experts, and other research sources. In addition, meticulous data collection and assessment were carried out by the review authors to avoid errors. This systematic review provides information that all three lasers are safe and effective in treating keloid scars, especially in combination with other therapies. Further trials with larger sample sizes and prolonged follow-ups that directly compare the efficacy and safety of different lasers are needed to allow practitioners to choose the best course of treatment from a list of possibilities based on evidence.

Table 4.2 Characteristics of the scars

Study	**Scar type**	**Etiology**	**Location**	**Scar age & size**
Cho S (2010)	HTS & Keloid	Acne (n=11), surgery (n=4), smallpox vaccination (n=3), trauma (n=2) and burn (n=1)	Jaw, shoulder, elbow, forearm, chest wall, foot, back	7.8 (1-25 years)

Table 4.2 Characteristics of the scars (cont.)

Study	**Scar type**	**Etiology**	**Location**	**Scar age & size**
Madan V (2011)	Keloid	NR	Females: shoulders 46%, chest 19%, head and neck 12%, back 10%, extremities 7%, trunk 6%. Male: back 29%, chest 28%, extremities 20% shoulders 18%, face/scalp/neck 4% and trunk 1%	NR
Akaishi S (2012)	HTS & Keloid	operation (n=5), Acne (n=7), BCG vaccination (n=1), Insect bite (n=1), Trauma (n=2)	Shoulder (n=5), pubic (n=2), anterior chest (n=7), lower jaw (n=2)	5 to 240 months (54.56 ± 59.60 months)
Yang Q. (2012)	Keloid	Folliculitis 84.62%	Chest or scapular area	NR
Anthony Rossi (2013)	Keloid	NR	NR	From 1 year to decades (duration), > 1 cm in thickness and length

Table 4.2 Characteristics of the scars (cont.)

Study	**Scar type**	**Etiology**	**Location**	**Scar age & size**
Sachiko Koike (2014)	HTS and keloid	Acne, vaccination	keloid = anterior chest, upper arm, scapula	> 1 year
O. A. Azzam (2016)	HTS & Keloid	NR	Head and neck, upper limb	Mean duration of scar 4.62 years (0.167 - 20 years). HTS and keloid of any size
Al-Mohamady A.E (2016)	HTS and keloid	burn 30%, trauma 50%, surgery 5%, not certain cause of scar 15 %	NR	2-10 months (7 ± 2.1 months)
Chen X.-E.(2017)	Keloid	NR	Face and neck 4.7%,trunk 67.8%, proximal extremities 22.5%, distal extremities 5%	32.9 ± 27.6 months, at least 10 mm in length
Sunil Srivastava (2018)	Keloid	Trauma (n=18), infection (n=17), burn (n=15), surgery (n=10)	Pre-sternal area (n=24), trunk (n=14) , extremities (n=13), face (n=9)	> 6 months and < 2 years, size 0.5 to 5cm in greatest dimension

Table 4.2 Characteristics of the scars (cont.)

Study	**Scar type**	**Etiology**	**Location**	**Scar age & size**
Alexander Sajin (2019)	HTS & Keloid	Trauma 69.64%, acne 16.07%, spontaneously 14.28%	Face 8.9%, foot 1.8%,forearm 5.4%, hand 5.4%,leg 1.8%, shoulder 5.4%	6 months to 20 years (most lesions were 1-3 years seen in 39.3%, 4-6 years seen in 21.4% of the participants)
Shereen O. Tawfic (2020)	HTS & Keloid	Scalding, burns, history of cuts at the site of involvement, post-acne scars	Upper extremities, lower extremities, trunk, mixed sites (scars affecting upper extremities and trunk)	0.5 - 30 years (mean 8.84 ± 7.65 years)
Chi Xu (2020)	Keloid	Spontaneous formation(33.3), acne(33.3%), surgery (23.8%), trauma (4.8%), chicken pox(4.8%)	Chest (61.1%), scapula (22.2%), back (16.7%)	0.5 - 20 years (mean 4.17 years)
Nadia H. Sahib (2020)	HTS & Keloid	burn (n=7) , surgery (n=4), wound healing (n=2) and acne (n=8), TCA (n=1)	HTS (Cheek, Neck, Chest, Back, Axilla, Limb) Keloid (Cheek, Chest)	HTS 1 - 30 cm, Keloid scar 1 - 5 cm, scar age 6 months to 20 years

Table 4.2 Characteristics of the scars (cont.)

Study	**Scar type**	**Etiology**	**Location**	**Scar age & size**
Khattab F.M (2020)	Keloid	Trauma (n=18), burn (n=12), spontaneously (n=10)	Extremities (n=19), trunk (n=6), ear (n=11), face (n=4)	6 months – 20 years
Wang J (2020)	Refractory keloids	Burn (n=5) , local infection (n=7), trauma (n=3), surgery (n=9), ear piercing (n=2), folliculitis (n=10), Unknown (n=5)	Anterior chest (n=19), Suprapubic region (n=6), Clavicle (n=2), Ear (n=3), Neck (n=3), Mandible (n=2), Back (n=3), Shoulder (n=1), Abdomen (n=1), Arm (n=1)	23 - 56 months
Solima M. (2021)	Keloid	Spontaneous formation (11.11%), surgical scar (14.0%), injury (20.0%), acne (11.11%), burn (44.4%)	Upper limb 41%, lower limb 36%, abdomen 13%, face 10%	9.0 ± 0.2 (6 - 12 months)
Alhamzawi N.K. (2021)	Keloid	Surgery (n=11), ear piercing (n=5), burn (n=4), trauma (n=2), aggressive	Chest 36.3%, Shoulders 25%, Back 15.9%, Ear 15.9%, Upper arms 6.8%	14 - 48 months (mean 31.25 ± SD 11.6 months)

Table 4.2 Characteristics of the scars (cont.)

Study	Scar type	Etiology	Location	Scar age & size
		salabrasion for tattoo removal (n=2), family history (n=3)		
Heba Ramadan (2021)	HTS & Keloid	Burn 50%, surgery 5%, vaccination 10%, after laser 5%,spontaneous 10%, accident 10%,injury 10% in Laser + Injection group Burn 55%, surgery 5%, vaccination 5%, accident 10%, injury 5% in Laser only group	Arm 15%, Forearm 15%, Abdomen 20%, Shoulder 10%, Upper lip 5%, Neck 10%, Chest 5%, Ear 5%, Thigh 5%, Face 5%, Hand 5% in Laser + Injection group Arm 10%, Shoulder 10%, Upper lip 5%, Neck 15%, Chest 20%,Thigh 5%, Face 15%, Hand 10%, Elbow 5%, Foot 5% in Laser only group	NR
El-Hamid El-Azhary EA (2022)	Keloid	Trauma, surgery, spontaneous and ear piercing	Ear, chest, back	> 6 months

Table 4.2 Characteristics of the scars (cont.)

Study	**Scar type**	**Etiology**	**Location**	**Scar age & size**
Tawaranurak N. (2022)	Keloid	Acne (n=4), Infection (n=1), Piercing(n=1), Surgery (n=8), Trauma (n=6), Vaccination (n=2)	Chest (n=11), extremities (n=4), abdomen (n=3), ear (n=2), breast (n=1), flank (n=1)	NR

HTS = hypertrophic scar, NR= not reported, TCA = trichloroacetic acid

Table 4.3 Characteristics of study, patient demographics, and quality of study

Study	**Location**	**Study design**	**Sample Size**	**Age**	**Fitzpatrick skin type**	**Number of keloids**	**OCEBM Quality Rating**
Cho S (2010)	Korea	Retrospective analysis (HTS & Keloid)	12 (10 males, 2 females)	23.8 (21 - 33)	IV	NR	Level 3
Madan V (2011)	UK	Retrospective case series (Keloids)	99 (41 males, 58 females)	NR	NR	755	Level 4
Akaishi S (2012)	Japan	Prospective (HTS & keloid)	22 (4 males,18 females)	34.95 (mean age)	NR	16	Level 3
Yang Q. (2012)	China	Randomized control study (Keloid)	26 (12 males, 14 females)	20 - 40 (26.35 ± 6.50 years)	III, IV	NR	Level 2

Table 4.3 Characteristics of study, patient demographics, and quality of study (cont.)

Study	**Location**	**Study design**	**Sample Size**	**Age**	**Fitzpatrick skin type**	**Number of keloids**	**OCEBM Quality Rating**
Anthony Rossi (2013)	US	Retrospective analysis (Keloid)	44	31.00 (8.34) for laser, 31.93 (12.74) for Laser + IL TAC, 38.06 (11.96) for IL TAC	I-VI	NR	Level 3
Sachiko Koike (2014)	Japan	Retrospective cohort study (HTS & Keloids)	102 (23 males, 79 females)	34.8 years (mean age)	NR	64	Level 3

Table 4.3 Characteristics of study, patient demographics, and quality of study (cont.)

Study	Location	Study design	Sample Size	Age	Fitzpatrick skin type	Number of keloids	OCEBM Quality Rating
Al-Mohamady A.E (2016)	Egypt	Prospective, randomized, blinded, single-center, non-controlled, comparative, split-scar trial (HTS & Keloids)	28 (9 males,11 females)	5 - 35 (22.6 ± 8.1)	III, IV	9	Level 2
O. A. Azzam (2016)	Egypt	Prospective randomized intra-individual comparative clinical trial (HTS & Keloids)	30 (18 keloids: 11 males & 7 females, 12 HTS: 4 males & 8 females)	31.4 ± 11.1 years (keloid group)	II-VI	18	Level 2

Table 4.3 Characteristics of study, patient demographics, and quality of study (cont.)

Study	Location	Study design	Sample Size	Age	Fitzpatrick skin type	Number of keloids	OCEBM Quality Rating
Chen X.-E. (2017)	China	Randomized controlled trial (Keloids)	69	26.7± 7.5 years	NR	NR	Level 2
Sunil Srivastava (2018)	India	Prospective single-blind, randomized parallel-group study (Keloids)	60 (29 males, 31 females)	12 - 50 years	NR	NR	Level 2
Alexander Sajin (2019)	India	Comparative study (HTS & Keloids)	50 (38 males, 12 females)	> 18 years	IV, V	46	Level 3
Shereen O. Tawfic (2020)	Egypt	Intra-individual randomized controlled clinical trial (HTS & Keloids)	30 (8 males, 22 females)	18 - 49 years (mean age 25.97 ± 9.32 years)	II-IV	10	Level 2

Table 4.3 Characteristics of study, patient demographics, and quality of study (cont.)

Study	**Location**	**Study design**	**Sample Size**	**Age**	**Fitzpatrick skin type**	**Number of keloids**	**OCEBM Quality Rating**
Chi Xu (2020)	China	Prospective study (Keloids)	21(9 males, 12 females)	17 - 51 years	NR	54	Level 3
Nadia H. Sahib (2020)	Iraq	Randomized control study (HTS & Keloids)	22 (13 males, 9 females)	14 - 37years	NR	NR	Level 2
Wang J (2020)	China	Prospective clinical trial (Refractory keloids)	41 (20 males, 21 females)	27.4 years (6 - 62 years)	NR	NR	Level 3
Khattab F.M (2020)	Egypt	Comparative study (Keloid)	40 (20 males and 20 females)	18 - 70 years	NR	56	Level 3

Table 4.3 Characteristics of study, patient demographics, and quality of study (cont.)

Study	**Location**	**Study design**	**Sample Size**	**Age**	**Fitzpatrick skin type**	**Number of keloids**	**OCEBM Quality Rating**
Heba Ramadan (2021)	Egypt	Prospective simple randomization study (HTS & Keloids)	40	27.35 ± 8.46 in Nd: YAG laser followed by Intralesional Bleomycin and 28.40 ± 9.79 in Nd: YAG laser alone group	NR	NR	Level 2
Alhamzawi N.K. (2021)	Iraq	Prospective open-label interventional trial (Keloids)	22 (14 males, 10 females)	16 - 58 years (mean 24.25 ± SD 9.49 years)	III-V	44	Level 3
Solima M. (2021)	Egypt	Simple randomized, single-blinded comparative study (Keloid)	45 (20 males, 25 females	19 - 44 years (30.5 ± 6.8) years	II-IV	NR	Level 2

Table 4.3 Characteristics of study, patient demographics, and quality of study (cont.)

Study	Location	Study design	Sample Size	Age	Fitzpatrick skin type	Number of keloids	OCEBM Quality Rating
El-Hamid El-Azhary EA (2022)	Egypt	Comparative study (Keloid)	45(21 males, 24 females)	20 - 55 years (33.69 ± 11.02)	NR	NR	Level 3
Tawaranurak N. (2022)	Thailand	Prospective randomized controlled study (Keloid)	22 (8 males, 14 females)	44.8 ± 19.9 years (Laser + topical TAC), 42.6 ± 18.3 (Intralesional TAC alone)	NR	NR	Level 2

HTS= hypertrophic scar, NR= not reported, TAC = trichloroacetic acid, Nd: YAG = neodymium-doped yttrium aluminum garnet

Table 4.4 Pulsed dye laser

Authors	**PDL laser**	**No. of treatments and treatment interval**	**Follow-up period**	**Intervention**		**Laser setting**
				1	**2**	
Madan et al., 2011	595 nm PDL	3 sessions of treatments spaced at 6-8 weeks intervals	6 months	PDL alone	PDL in conjunction with ILTAC (10 mg or 40 mg/ml)	4 -15 J/cm², 7 mm spot size, 1.5 ms pulse duration
Yang et al., 2012	595 nm PDL (Vbeam, Candela Corporation, Wayland MA)	3 sessions of PDL treatment at 3-4 weeks interval	3 weeks	PDL		10 J/cm², 7mm spot size, 1.5 ms pulse duration, single pass without pulse stacking

Table 4.4 Pulsed dye laser (cont.)

Authors	**PDL laser**	**No. of treatments and treatment interval**	**Follow-up period**	**Intervention**		**Laser setting**
				1	**2**	
Al-Mohamady et al., 2016	595 nm PDL laser (Synchro VasQ, Deka, Florece, Italy), 1064 nm LP Nd: YAG laser (Synchro Replay Excellium HP, Deka, Florence, Italy)	6 treatment sessions with 4weeks interval	1 month	PDL alone	Nd: YAG laser	595 nm PDL using 7-9 J/cm², 10 mm spot size, 1.5 ms pulse duration, second part was treated using 1064 nm LP Nd: YAG laser using 30-35 J/cm², 14 mm spot size, 20 ms pulse duration

Table 4.4 Pulsed dye laser (cont.)

Authors	**PDL laser**	**No. of treatments and treatment interval**	**Follow-up period**	**Intervention**		**Laser setting**
				1	**2**	
Khattab et al., 2020	595 nm PDL	IL Verapamil alone for every 3 weeks for a maximum of 8 sessions or until complete flattening of the scar; PDL + IL Verapamil for a minimum of 4 sessions at 6 - 8 weeks intervals	6 months	PDL followed by IL Verapamil	IL Verapamil 2.5 mg/ml	4-15 J/cm², 7 mm spot size, 1.5 ms pulse duration

Table 4.4 Pulsed dye laser (cont.)

Authors	PDL laser	No. of treatments and treatment interval	Follow-up period	Intervention		Laser setting
				1	2	
Xu et al., 2021	Dual wavelength (585 nm PDL and 1064 nm Nd: YAG) Cynergy Laser system	4 treatment sessions with 4 weeks to 6 weeks intervals.	1 month	PDL followed by Nd: YAG laser		First pulse of PDL using 8.0 J/cm², 7 mm spot size, 2.0 ms pulse duration followed by a second pulse of Nd: YAG laser using 45 J/cm², 7 mm spot size, 15 ms pulse duration with a minimum delay of 250 ms

PDL = pulsed dye laser, LP - Nd: YAG = long pulsed neodymium-doped yttrium aluminum garnet, IL TAC = intralesional triamcinolone acetonide

Table 4.5 1064 nm Nd: YAG laser

Authors	**Nd: YAG laser**	**No. of treatments and treatment interval**	**Follow-up period**	**Intervention**			**Laser setting**
				1	**2**	**3**	
Cho et al., 2010	1064 nm QS Nd: YAG laser (Lutronic, Goyang, Korea)	several sessions at 1– 2 weeks intervals & the mean number of treatment sessions was 7.8 (range 5 -10) which was determined according to the treatment response, patient satisfaction, and demand	3 months	1064 nm QS Nd: YAG laser alone			1.8-2.2 J/cm², 7 mm spot size, and 5-6 passes with appropriate overlapping (roughly 5-15%) without the need for LA

Table 4.5 1064 nm Nd: YAG laser (cont.)

Authors	**Nd: YAG laser**	**No. of treatments and treatment interval**	**Follow-up period**	**Intervention**			**Laser setting**
				1	**2**	**3**	
Akaishi et al., 2012	Long-pulsed 1064 nm Nd: YAG laser (Genesis, Cutera Inc, Brisbane, California)	patients received 14.05 exposures on average every 3-4 weeks. Betamethasone butyrate propionate or clobetasol propionate ointment was administered at 0.1 g/cm² for 2-3 days after the treatment to reduce the chance of bulla developing after irradiation.	NR	LP-Nd: YAG laser followed by topical steroid			14 J/cm², 5 mm spot size, 0.3 ms pulse duration, repetition rate of 10 Hz. Laser irradiation was in non-contact mode by applying from 2-3 cm above the skin surface in a zigzag fashion

Table 4.5 1064 nm Nd: YAG laser (cont.)

Authors	**Nd: YAG laser**	**No. of treatments and treatment interval**	**Follow-up period**	**Intervention**			**Laser setting**
				1	**2**	**3**	
Rossi et al., 2013	1064 nm Nd: YAG laser	An average of 7 treatments every 3 weeks were done for each patient in laser only group. Laser treatments were done every 3 weeks with the IL TAC injected before the laser treatment for a total of six sessions for each patient in combination group	NR	1064 nm Nd: YAG laser only	1064 nm Nd: YAG laser + IL TAC	IL TAC 10 mg/cc, total volume of 3 cc per session	13-18 J/cm², 5 mm spot size, 300 µs pulse duration and a total of 2000 pulses delivered in the "paint" mode.

Table 4.5 1064 nm Nd: YAG laser (cont.)

Authors	**Nd: YAG laser**	**No. of treatments and treatment interval**	**Follow-up period**	**Intervention**			**Laser setting**
				1	**2**	**3**	
Koike et al., 2014	Long-pulsed 1064 nm Nd: YAG laser (Cutera, Brisbane, Calif.)	treated every 3-4 weeks for 1 year with a LP - Nd: YAG laser in contact mode	6 months	Nd: YAG laser alone			65-75 J/cm², 5 mm spot size, 250 μs pulse duration, and a repetition rate of 2 Hz. Each session consisted of 3 passes unless the patient felt strong pain at the second pass

Table 4.5 1064 nm Nd: YAG laser (cont.)

Authors	**Nd: YAG laser**	**No. of treatments and treatment interval**	**Follow-up period**	**Intervention**			**Laser setting**
				1	**2**	**3**	
Chen et al., 2017	1064 nm Nd: YAG (Lumenis One;Lumenis, Santa Clara , CA, USA)	3 sessions at one month interval for all 3 groups	NR	IL Diprospan	IL Diprospan 1ml + 5-FU 0.5ml	IL Diprospan 1 ml + 5-FU 0.5 ml+ 1064 nm Nd: YAG alone	90-100 J/cm², 6 mm spot size, 12 ms pulse, with a single pass of spots overlapping 5 - 10% without cooling

Table 4.5 1064 nm Nd: YAG laser (cont.)

Authors	**Nd: YAG laser**	**No. of treatments and treatment interval**	**Follow-up period**	**Intervention**			**Laser setting**
				1	**2**	**3**	
Ramadan et al., 2021	1064 nm Nd: YAG laser	every 4 weeks for a maximum of 5 sessions	6 months	Nd: YAG laser + IL Bleomycin 0.1ml (blenoxane vial) (1.5 IU/ml)	Nd: YAG laser alone		45-50 J/cm², 5 - 10 mm spot size (according to the thickness of the scar), 5 ms pulse duration

QS Nd: YAG = quality switch neodymium-doped yttrium aluminum garnet, LA = local anesthesia, IL TAC = intralesional triamcinolone acetonide, 5-FU = 5-fluorouracil, NR = not reported

Table 4.6 10600 nm Fractional Carbon Dioxide Laser

Authors	**Fractional CO_2 laser**	**No. of treatments and treatment interval**	**Follow-up period**	**Treatment**			**Laser setting**
				1	**2**	**3**	
Azzam et al., 2016	Fractional CO_2 laser (DEKA, SMARTXIDE DOT, Italy)	total of 4 sessions, 6weeks apart	6 months	Fractional CO_2 laser			30 W, 1000 µs dwelling time, and 800 µs spacing, stack 4
Srivastava et al., 2019	Fractional CO_2 laser	every 3 weeks for 24 weeks or till scar flattening occurred, whichever was earlier	NR	Fractional CO_2 laser alone	IL 2 ml of TAC (40 mg/ml)	IL 2 ml of Verapamil (2.5 mg/ml)	30-50 mJ, spot density of 25 spots/cm²

Table 4.6 10600 nm Fractional Carbon Dioxide Laser (cont.)

Authors	**Fractional CO_2 laser**	**No. of treatments and treatment interval**	**Follow-up period**	**Treatment**			**Laser setting**
				1	**2**	**3**	
Alexander et al., 2019	Fractional CO_2 laser (Acupulse from Lumenis)	Minimum of four sessions, 28 days apart	4 weeks	Fractional CO_2 laser therapy followed by IL TAC 10 mg/ml	IL TAC		Single pass of 5-30 mJ, 5% to 30% density for deep scan and 50-80 mJ, a density 40% to 60% for superficial scan

Table 4.6 10600 nm Fractional Carbon Dioxide Laser (cont.)

Authors	**Fractional CO_2 laser**	**No. of treatments and treatment interval**	**Follow-up period**	**Treatment**			**Laser setting**
				1	**2**	**3**	
Tawfic et al., 2020	Fractional CO_2 laser, LP-Nd: YAG	4 laser sessions at 4-6 weeks intervals	1 month	CO_2 laser alone	LP-Nd: YAG laser alone	Fractional CO_2 laser followed by Nd: YAG laser after half an hour	FCL 20 W power, 1000 µs dwell time, 800 µs spacing, and stack of LP-Nd: YAG laser with 40 J/cm², 5mm spot size, and 0.3 ms pulse duration in a focused mode for 3 passes

Table 4.6 10600 nm Fractional Carbon Dioxide Laser (cont.)

Authors	**Fractional CO_2 laser**	**No. of treatments and treatment interval**	**Follow-up period**	**Treatment** 1	2	3	**Laser setting**
Sahib et al., 2020	Fractional CO_2	every month sessions with a total course of 4 months	4 months	Fractional CO_2 laser followed by IL TAC	IL TAC alone		Energy used by FCL was adjusted by the site of the scar. Five minutes following the laser session, an injection of IL TAC was done until the blanching of the scar

Table 4.6 10600 nm Fractional Carbon Dioxide Laser (cont.)

Authors	**Fractional CO_2 laser**	**No. of treatments and treatment interval**	**Follow-up period**	**Treatment** 1	2	3	**Laser setting**
Wang et al., 2020	Fractional CO_2 laser (Lumenis Corporation, Santa Clara,USA) in scanner mode	8 treatment sessions at 4 weeks intervals	24 months	Ultrapulse Fractional CO_2 laser followed by application of topical TAC (40 mg/ml) occluded under a transparent film dressing for 4 hours			DEEP FX, 17.5-22.5 J/cm² with 10% density, and frequency 300 Hz. To avoid overlapping, the shape of the spots varied according to the keloid shapes.

Table 4.6 10600 nm Fractional Carbon Dioxide Laser (cont.)

Authors	**Fractional CO_2 laser**	**No. of treatments and treatment interval**	**Follow-up period**	**Treatment**			**Laser setting**
				1	**2**	**3**	
Soliman et al., 2021	Fractional CO_2 laser (Wonteck Sahil Fractional CO_2 laser, Daejeon, Korea), LP-Nd: YAG (Elite Plus Cynosure long-pulsed 1064 nm laser, Westford, Massachusetts, USA)	every month for a maximum of 4 sessions	2 months	Fractional CO_2 laser only	LP-Nd: YAG laser only	FCL followed by LP-Nd: YAG with a 15-minute interval	FCL 40-50 mJ density 25 spots/cm², 3 passes of stacking in each session. LP-Nd: YAG laser with 65-75 J/cm², 5 mm spot size, 20 ms pulse duration, 2 Hz repetition rate, 3 passes

Table 4.6 10600 nm Fractional Carbon Dioxide Laser (cont.)

Authors	**Fractional CO_2 laser**	**No. of treatments and treatment interval**	**Follow-up period**	**Treatment**			**Laser setting**
				1	**2**	**3**	
Alhamzawi, 2021	Fractional CO_2 laser	1-month interval for a maximum of 6 sittings.	NR	Fractional CO_2 laser followed by 5-FU injection			Fractional CO_2, 20 mJ, 0.6 mm distance, moving time 1s perpendicularly followed by 1ml/cm²/lesion of 5-FU (50mg/ml) intralesional with a maximum dose of 150 mg/ session

Table 4.6 10600 nm Fractional Carbon Dioxide Laser (cont.)

Authors	**Fractional CO_2 laser**	**No. of treatments and treatment interval**	**Follow-up period**	**Treatment**			**Laser setting**
				1	**2**	**3**	
El-Hamid El-Azhary et al., 2022	Fractional CO_2 laser	4 sessions 4 weeks apart	2 months	FCL alone	FCL was followed immediately by TAC at a dose of 0.25 ml/cm³ for keloid < 3 cm and 0.5 ml/cm³ for keloid >3 cm then occluded using transparent film dressings for 3 hours	FCL followed immediately by TAC 20% application then occluded for 3 hours	20-25 J, timing 300 ms and spacing 350 mm, stack 1-2

Table 4.6 10600 nm Fractional Carbon Dioxide Laser (cont.)

Authors	**Fractional CO_2 laser**	**No. of treatments and treatment interval**	**Follow-up period**	**Treatment**			**Laser setting**
				1	**2**	**3**	
Tawaranurak et al., 2022	Fractional CO_2 laser (eCO_2, Lutronic Co.Ltd, Seoul, Korea)	average no. of treatment in laser + topical TAC group was 10.5 ± 2.6 and 6.3 ± 3.0 in IL TAC alone group	every 2-month interval for 1 year	FCL followed by TAC was applied over the scar immediately & occluded under a transparent film dressing for 30 minutes	IL TAC alone (40 mg/cm³) diluted (1:1) with 1% xylocaine + adrenaline (1:200000)		power 30 W, pulse energy 30 mJ, and density 200 spots/cm² in static mode, beam size 120 µm (mm)

FCL = fractional carbon dioxide laser, IL TAC = intralesional triamcinolone acetonide, 5-FU = 5-fluorouracil, TAC = trichloroacetic acid, NR= not reported

Chapter 5

Conclusion and Recommendations

5.1 Conclusion

The effect of laser treatment on the severity of hypertrophic and keloid scars is now the subject of little research. We are unable to determine if lasers are a better option overall for treating hypertrophic and keloid scars than conventional procedures due to the heterogeneity of the research and inconsistent findings. To further guide future clinical practice and better understand the possible effects of laser therapy for certain scar types, more high-quality trials with long-term follow-up and the incidence of scar recurrence are required.

A range of therapeutic approaches have similar success rates for both keloid and hypertrophic scarring. The effectiveness of corticosteroid intralesional injection has been demonstrated to be on par with laser treatment, and it has withstood the test of time. Multiple factors can influence treatment selection such as physicians' experiences, treatments available, patients' prior knowledge, the size of the region to be treated, unsuccessful interventions in the past, and the significance of side effects are a few examples. When opting for laser therapy, we aim to utilize the best available laser system.

The results of this comprehensive review indicate that 585-595 nm pulsed dye laser, 1064 nm Nd: YAG laser, and 10600 nm fractional CO_2 laser either in conjunction with other therapies or laser alone therapy produced the greatest improvement in all scar features. The scar vascularity was the most prominent characteristic to improve with PDL, and this result was supported by measuring the blood perfusion with laser speckle contrast imaging (LSCI) where perfusion was significantly decreased after four treatment sessions in the Xu et al. study (Xu et al., 2021).

Regarding scar pliability, Soliman reported that fractional CO_2 laser and Nd: YAG lasers worked together to control keloids with fractional CO_2 laser being more effective than Nd: YAG laser and Nd: YAG being the least effective (Soliman et al., 2021). Moreover, the reduction in thickness of keloid after fractional laser treatment was approved by Color Doppler Ultrasound in El-Hamid El-Azhary et al. research (El-Hamid El-Azhary et al., 2022). The outcomes from all included studies were satisfactory, and the adverse effects were barely noticeable. Despite variations in the number of treatments and treatment settings applied, all trials using the laser produced an objective improvement in scar features.

Nonetheless, heterogeneity was seen in several areas, including scar age and size, scar location, follow-up, and treatment count. Considering this information as well as the vast variety of laser systems, judgments are made using the best available data. This finding requires validation by more prospective research and randomized controlled trials with a robust methodological design, well-defined scar features, and standardized and validated outcome measures.

5.2 Recommendations

Keloid scars were treated with a wide variety of laser equipment and techniques, leading to numerous comparisons, frequently with no data or evidence. Further randomized controlled trials (RCTs) evaluating laser treatment for treating the different types of scars are required, as this is a high-priority clinical decision issue in the area. Standardization of new research is necessary to ensure more consistent and trustworthy data for an accurate comparison of the findings. Study participants with the same phototype should be treated with the same laser device (e.g., 585-nm PDL), delivered with the same fluency, in an equal regimen for similar scars (e.g., the same scar age, size, and body region). Hypertrophic and keloidal scars, on the other hand, should be evaluated separately as they may respond differently to different treatment modalities due to their physiological differences. The follow-up period should be long enough to evaluate the long-term effects of laser therapy such as recurrence incidents, or even worsening following treatment.

We advise using verified and comparable assessment scales for scar features. The approved scar scale should assess both objective (ascertained using tools such as colorimeters, ultrasounds, graduated calipers, and blinded observers) and subjective (ascertained by participant opinion regarding the degree of improvement in scar severity, symptoms, cosmesis, pain during treatment, etc.) aspects. We consider the Vancouver Scar Scale (VSS) and the Patient and Observer Scar Assessment Scale (POSAS) to be suitable for subjective assessments. Furthermore, although quantitative metrics are important for assessing results, the VSS does not take into account the subjective nature of scarring's effect on quality of life. Using a spectrometer to evaluate erythema and pigmentation, a dial caliper for height, and a cutometer for pliability are the recommended methods for objective measures. Additionally, if a split-scar design is used, it could be helpful for future studies to leave treatment-free regions in between the treated scar segments to prevent a "spill-over" of the therapy from one scar segment to the other. Furthermore, the rate of scar recurrence during the follow-up periods and outcome data for the therapies being compared must be reported clearly and comprehensively.

In the setting of keloid scarring, high-quality randomized controlled studies are required to evaluate the combined effect of laser and conventional treatment as well as laser-assisted drug delivery systems. Research including a greater number of participants, extended periods of follow-up, and uniform assessment of results and side effects are necessary. Furthermore, to efficiently obtain as much information as feasible, future research may consider a factorial randomized controlled trial design.

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APPENDICES

APPENDIX A

List of Primary Search Strategy

List of the primary search strategy

1.PubMed

Date of search:6/9/2023

The number of results: 1058

Search strings	No. of results
((“Lasers, Dye”[Mesh] OR “pulsed dye laser*”[tw] AND keloid*[tw] OR“keloid scar*”[tw]) OR (“Lasers, Solid-State”[Mesh] OR “Nd:YAG laser*”[tw] AND keloid*[tw] OR “keloid scar*”[tw])) OR (“Lasers, Gas”[Mesh] OR “fractional carbon dioxide laser*”[tw] AND keloid*[tw] OR “keloid scar*”[tw])	1058

2. Scopus

Date of search:6/9/2023

Number of results: 263

Search strings	No. of results
(TITLE-ABS-KEY ((“keloid*” OR “keloid scar*”) AND “pulsed dye laser*”) OR TITLE-ABS-KEY ((“keloid*” OR “keloid scar*”) AND “Nd YAG laser*”) OR TITLE-ABS-KEY ((“keloid*” OR “keloid scar*”) AND “fractional carbon dioxide laser*”))	263

3. Cochrane Central Registered of Controlled Trials

Date of search: 6/9/2023

Number of results: 54

Search strings	**No. of results**
Keloid* AND “pulsed-dye lasers”	21
Keloid* AND “Nd: YAG lasers”	17
Keloid* AND “fractional carbon dioxide laser”	16

Records tracking

Record identified from PubMed	1058	
Record identified from Scopus	263	Without date range
Record identified from Cochrane	54	
Total records identified from databases	1375	

Records removed before the screening

1. Records removed for other reasons (studies before 2010):
    a. 345 (1058-713) PubMed
    b. 110 (263-153) Scopus — 472
    c. 17 (54-37) Cochrane
2. Duplicate records removed: 109 (903-794)
3. Records removed after Title search: 550 (794 - 244)

Total number of articles left for abstract screening: 244

Articles mentioning the following in the title were removed:

a) Keloid pathogenesis on the molecular level and other genetic trials with animals

b) Laser treatment on other diseases such as melasma, papulosis nigra, and other diseases

c) Other types of management of keloids such as TCA injection, 5-FU, and silicone gel sheet, radiation therapy, mesenchymal stem cell therapy, and mitomycin C without mentioning any laser therapy

d) Other types of lasers for keloid treatment e.g.: 1470 nm diode laser

e) Epidemiology of keloid

f) Hypertrophic scar without mentioning keloid

g) Other types of scars e.g., burn scar

Table 1 Manual Screening

Author	**Year**	**Title**	**Reason to exclude**
Lee SJ	2015	Combined treatment with botulinum toxin and 595nm pulsed dye laser in the treatment of erythematous scar	Case report
Tao J	2018	Treatment of burn scars in Fitzpatrick phototype III patients with a combination of PDL and non-ablative fractional resurfacing 1550nm Er: Glass/1972nm thulium laser devices	Case report does not mention keloid scar
Ouyang H-W	2018	Comparison of the effectiveness of PDL Vs PDL combined with ultra pulse fractional CO2 laser in the treatment of immature red hypertrophic scars	Hypertrophic scars
Kim DH	2014	A comparison of the scar prevention effect between CO2 fractional laser and PDL in surgical scars	Does not mention keloid (surgical scars of 2 weeks post Mohs surgery)

Table 1 Manual Screening (cont.)

Author	Year	Title	Reason to exclude
Keany TC	2016	Comparison of 532nm potassium titanyl phosphate laser and 595nm PDL in the treatment of erythematous surgical scars: a randomized, controlled, open-label study	Does not mention keloid, surgical scars only
Vranova J	2015	Comparison of quality of facial scars after single low-level laser therapy and combined low-level with high-level (PDL 595nm) laser therapy	Post-traumatic linear facial scar (does not mention keloids)
Gladsjo JA	2014	Treatment of surgical scars using a 595nm PDL using purpuric and non-purpuric parameters: a comparative study	Post-operative linear scar (does not mention keloids)
Lin JY	2011	A prospective, randomized controlled trial on the efficacy of fractional photothermolysis on scar remodeling	Hypertrophic scar
Jung JY	2011	Early Postoperative Treatment of Thyroidectomy Scars Using a Fractional Carbon Dioxide Laser	Not keloid scar/ Prevention

Table 2 Unretrieved Clear Studies

Authors	**Year**	**Title**	**Publication**
Kim W.I.; Heo J.; Kim S.; Cho M.K.	2020	The Effectiveness of Fractional Carbon Dioxide Laser plus Intralesional Triamcinolone Acetonide Compared with Intralesional Triamcinolone Acetonide Monotherapy for the Treatment of Keloid and Hypertrophic Scar: A Systematic Review and Meta-analysis	Review article
Potter K.; Konda S.; Ren V.Z.; Wang A.L.; Srinivasan A.; Chilukuri S.	2017	Techniques for optimizing surgical scars, part 2: Hypertrophic scars and keloids	Article
Potts J.L.; McLaughlin J.M.; Weeks D.W.; Branski L.K.; Norbury W.B.	2020	Nd: YAG Laser and Intense Pulsed Light (IPL) in the Treatment of Hypertrophic and Keloid Scar	Book chapter
Shokrollahi K.	2020	Laser management of scars	Book

APPENDIX B

Risk of Bias Assessment Forms

Risk of Bias Assessment Forms

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

1) Representativeness of the exposed cohort

a) truly representative of the average _____ (describe) in the community ★

b) somewhat representative of the average _____ in the community ★

c) selected group of users e.g. nurses, volunteers

d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort

a) drawn from the same community as the exposed cohort ★

b) drawn from a different source

c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure

a) secure records (e.g. surgical records) ★

b) structured interview ★

c) written self-report

d) no description

4) Demonstration that the outcome of interest was not present at the start of the study

a) yes ★

b) no

Comparability

1) Comparability of cohorts based on the design or analysis

a) study controls for _____ (select the most important factor)★

b) study controls for any additional factor★

(This criterion could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome

a) independent blind assessment★

b) record linkage★

c) self-report

d) no description

2) Was follow-up long enough for outcomes to occur

a) yes (select an adequate follow-up period for the outcome of interest)★

b) no

3) Adequacy of follow-up of cohorts

a) complete follow-up - all subjects accounted for★

b) subjects lost to follow-up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost)★

c) follow up rate < ____% (select an adequate %) and no description of those lost

d) no statement

CODING MANUAL FOR COHORT STUDIES

SELECTION

1) Representativeness of the Exposed Cohort

Item is assessing the representativeness of exposed individuals in the community, not the representativeness of the sample of women from some general population. For example, subjects derived from groups likely to contain middle-class, better-educated, health-oriented women are likely to be representative of postmenopausal estrogen users while they are not representative of all women (e.g. members of a health maintenance organization (HMO) will be a representative sample of estrogen users. While the HMO may have an under-representation of ethnic groups, the poor, and poorly educated, these excluded groups are not the predominant user of estrogen).

Allocation of stars as per the rating sheet

2) Selection of the Non-Exposed Cohort

Allocation of stars as per the rating sheet

3) Ascertainment of Exposure

Allocation of stars as per the rating sheet

4) Demonstration That Outcome of Interest Was Not Present at the Start of the Study

In the case of mortality studies, the outcome of interest is still the presence of a disease/ incident, rather than death. That is to say that a statement of no history of disease or incident earns a star.

COMPARABILITY

1) Comparability of Cohorts on the Basis of the Design or Analysis

A maximum of 2 stars can be allotted in this category.

Either exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.

There may be multiple ratings for this item for different categories of exposure (e.g. ever vs. never, current vs. previous or never)

Age = ☆, Other controlled factors = ☆

OUTCOME

1) Assessment of Outcome

For some outcomes (e.g. fractured hip), reference to the medical record is sufficient to satisfy the requirement for confirmation of the fracture. This would not be adequate for vertebral fracture outcomes where reference to X-rays would be required.

Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (x-rays, medical records, etc.)☆

a) Record linkage (e.g. identified through ICD codes on database records)☆
b) Self-report (i.e. no reference to original medical records or x-rays to confirm the outcome)
c) No description.

2) Was Follow-Up Long Enough for Outcomes to Occur

An acceptable length of time should be decided before the quality assessment begins (e.g. 5 yrs. for exposure to breast implants)

3) Adequacy of Follow-up of Cohorts

This item assesses the follow-up of the exposed and non-exposed cohorts to ensure that losses are not related to either the exposure or the outcome.

Allocation of stars as per the rating sheet

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)

Template for Completion

Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne on behalf of the RoB2 Development Group
Version of 22 August 2019

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Preliminary Considerations

Study details

Reference

Study design

X Individually-randomized parallel-group trial
☐ Cluster-randomized parallel-group trial
☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: Comparator:

Specify which outcome is being assessed for risk of bias	
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	

Is the review team's aim for this result…?

☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)

☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of adhering to intervention, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions

☐ failures in implementing the intervention that could have affected the outcome

☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)

☐ Journal article(s) with results of the trial

☐ Trial protocol

☐ Statistical analysis plan (SAP)

☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)

☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record) ☐ "Grey literature" (e.g. unpublished thesis) ☐ Conference abstract(s) about the trial ☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package) ☐ Research ethics application ☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research) ☐ Personal communication with trialist ☐ Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signaling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y / PY / PN / N / NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y / PY / PN / N / NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Signaling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		NA / Y / PY / PN / N / NI
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA / Y / PY / PN / N / NI
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y / PY / PN / N / NI
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Signaling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA / Y / PY / PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signaling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA / Y / PY / PN / N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signaling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		Y / PY / PN / N / NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		NA / Y / PY / PN / N / NI

Domain 4: Risk of bias in measurement of the outcome (cont.)

Signaling questions	Comments	Response options
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signaling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		Y / PY / PN / N / NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		Y / PY / PN / N / NI
5.3 ... multiple eligible analyses of the data?		Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Biography

Name	Su Thet Zin
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