Efficacy of Fractional Carbon Dioxide Laser (FCO₂) with Intralesional 5-Fluorouracil (5-FU) in the Treatment of Keloids

Nabeel Kadhim Alhamzawi
Department of Dermatology, Diwaniyah Teaching Hospital, Diwaniyah, Iraq

Abstract

Context: Managing keloids remains a challenge in clinical practice. Many therapeutic options are available, but none is universally accepted or without recurrence. Therefore, an effort is required to choose the treatment with maximal outcomes. Aims: To evaluate the effectiveness of combining fractional carbon dioxide (FCO₂) laser and intralesional 5-fluorouracil (5-FU) for the treatment of keloids. Materials and Methods: In this prospective open-label study, 24 patients received FCO₂ laser treatment, started at baseline, for a total of six sittings. The patients also received 1 mL/cm²/keloid of 5-FU (50 mg/mL) intralesionally, following irradiation, at identical time points. The primary outcome evaluated was the clinical response concerning height, pliability, vascularity, and pigmentation, using the Vancouver Score Scale (VSS). Adverse reactions and recurrences were recorded as secondary outcomes. Results: A significant reduction was observed in the VSS in terms of pliability and height after three treatment sessions. The mean VSS reduction was 65%, from 8.45 ± SD 0.93 at baseline to 3 ± SD 1.8 one month after the last treatment (P < 0.05). Most patients (79.1%; n = 19) showed a satisfactory response to treatment, with 57.8% (n = 11) achieving an excellent result. Adverse reactions included post-inflammatory hyperpigmentation in four patients and ulceration in two. Recurrences were reported in 21% of the patients who responded well. Conclusions: Combination therapy with FCO₂ laser and intralesional 5-FU showed a promising effect in the treatment of resistant keloids, with an acceptable safety profile and low recurrence rate.

Keywords: 5-Fluorouracil, fractional CO₂ laser, intralesional, keloid

INTRODUCTION

Keloid is a firm growth that results from abnormal wound healing in response to trauma or inflammation. Genetic and environmental factors may contribute to the development of keloids.[1] They are seen most commonly on the presternal areas, shoulders, upper back, earlobes, but they can occur anywhere. Keloids are firm, fibrous nodules, red to dark brown, and sometimes accompanied by pain or severe itching.[2] The best treatment is prevention in patients with predisposed risks. The therapeutic strategies include pressure therapy, topical silicone, radiation, intralesional corticosteroids, interferon, fluorouracil, and laser.[3,4] Nonablative types of lasers include 980-diode, Nd: Yag, and pulse dye laser have been investigated in the treatment of keloids with conflicting results.

5-FU is a fluorinated pyrimidine analog with antimetabolite activity, and both in vitro and in vivo experiments have shown that 5-FU can inhibit fibroblastic proliferation. Moreover, it has an inhibitory effect on TGF-β induce expression of the type 1 collagen gene and is believed to reduce postoperative scarring by decreasing fibroblast proliferation.[5-7]

Ablation of keloids with a fractional CO₂ laser (10,600 nm) can result in selective thermolysis of the dermal layer of the skin by creating microthermal zones MTZ. It increases the temperatures of skin layers to 70°C, resulting in denaturation and irreversible coagulation of dermis proteins, without affecting the epidermal layer.[8,9]
The surrounding healthy tissue helps in the remodeling, starting with a molecular cascade. Heat shock proteins, metalloproteinases, and inflammatory cytokines are activated during the healing process 48h following laser to compensate the vaporized columns with epidermal cells and restoring skin continuity.[10,11] Collagen remodeling results in the formation of new collagen with a decrease of collagen type I and an increase in type III.[12] The newly formed collagen type III has the ability to change the architecture of the dermis by increasing pliability, decreasing thickness, and improving molecular function.[12,13] Thus, it leads to the improvement of the surface of unstable chronic scars.[13-15] The present study aimed to evaluate the efficacy and safety of combining fractional CO2 laser and intra-lesional 5-FU for the treatment of keloids.

Subjects and Methods

An open-label prospective intervention trial was carried out among 24 patients to evaluate the efficacy and safety of FCO2 laser and intralesional 5-FU for the treatment for keloids. Approval was obtained from the local medical committee and written consent signed by all participants.

The inclusion criteria were
- Clinically diagnosed keloids
- Duration of keloids >1 year
- Patient age ranged from 18 to 65 years
- A healthy person who has no serious illness
- Those willing for treatment and regular follow-up
- No topical or intralesional therapy for the last 6 months.

The exclusion criteria include
- Patients <18 years and elderly
- Patients not willing to regular follow-up
- Medical illness of bone marrow, liver, and renal diseases
- Pregnant and lactating women
- Those who received topical or intralesional therapy within the last 6 months.

In total, 24 patients, each with one to three keloid scars, were enrolled for this study. The patient received 1 mL/cm2 /lesion of 5-FU (50 mg/mL) intralesionally, with a maximum dose of 150 mg/session. The treatment was given with a 1-month interval, for a maximum of six sittings. Topical lidocaine ointment (Emla) was applied 30 min before the treatment, to achieve local anesthesia. Each keloid was irradiated with FCO2 laser, fluence 20 mJ, distance 0.6 mm, moving time 1 s, perpendicularly. 5-FU (1 mL/cm2) was infiltrated into each lesion until complete blanching observed, using a 27-gauge syringe.

Analysis of laboratory profiles was done to monitor the changes in the liver, renal, and bone marrow functions before and every month after the procedure.

Evaluation of the response to the treatment was subjectively made using VSS, which incorporates the subsequent parameters (height, pliability, vascularity, and pigmentation). The height was measured using a caliper. Pliability was evaluated by palpation and labeled as soft, semi-solid, and solid. Vascularity was labeled as normal, pink, red, and purple, and pigmentation was labeled as hypopigmented, skin color, and hyperpigmented by inspection. The evaluation was done at four points: the baseline, 2 months, 4 months, and 6 months. The objective assessment of pain and pruritus was done at an equivalent time.

The response was measured by calculation of the percentage of changes in VSS before and after treatment, and labeled as follows: 0 = No change, 1–25% = poor, 26–50% = good, 51–75% = very good, 76–100% = excellent. The satisfactory result was assigned for patients who achieved >50% changes in VSS, and unsatisfactory result for those exhibited <50%. Adverse reactions were recorded during and after treatment, and follow-up continued for one year to assess the recurrence rate.

Vancouver score scale

A tool evaluated the changes in the appearance of the scars, using the parameters such as height, vascularity, pliability, and pigmentation to determine the score. The maximum score is 13, calculated as follows: pliability 0–5, height 0–3, vascularity 0–3, and pigmentation 0–2. Clinical improvement in the scar was assessed by decreasing the mean values of the score.[16,17]

Table 1: Demographic and clinical data

| Demographic                  | n (%) |
|------------------------------|-------|
| Number                       | 24    |
| Age                          | 16–58 |
| Mean                         | 24.25 |
| Gender (M/F)                 | 14/10 |
| Ratio                        | 1.4/1 |
| Number of keloids            | 44    |
| 8 patients                   | 1 for each |
| 12 patients                  | 2 for each |
| 4 patients                   | 3 for each |
| Duration of disease          | 14–48 months |
| Mean                         | 31.25 ± SD |
| 11.6                         |

Fitzpatrick skin
- Type III: 1 (4.16)
- Type IV: 19 (79.1)
- Type V: 4 (16.6)

Etiology
- Surgery: 11
- Ear piercing: 5
- Burn: 4
- Trauma: 2
- Salabrasion: 2
- Family history: 3 (12.5)
Data were analyzed using SPSS software version 26, by IBM, Chicago, USA. Data were defined as mean, standard deviation, number, and percentage. A paired \( t \)-test was used to study the rate of changes in the VSS before and after treatment. Spearman’s correlation was used to determine the association between the changes in the VSS and patient age and duration of the keloid. \( P < 0.05 \) was considered significant.

**RESULTS**

Twenty-four patients were enrolled in this study, aged from 16 to 58 years (mean 24.25 ± 9.49 years). The sex ratio was 1.4:1, with 14 males and 10 females.

| Table 2: Distribution of keloids among patients |
|-----------------------------------------------|
| keloids/patient | Male | female | % |
| One             | 5    | 3      | 33.3 |
| Two             | 7    | 5      | 50  |
| Three           | 2    | 2      | 16.6 |

| Table 3: Locations of keloids on the body |
|------------------------------------------|
| Site          | No. of keloids | %  |
| Chest         | 16             | 36.3|
| Shoulders     | 11             | 25  |
| Back          | 7              | 15.9|
| Ear           | 7              | 15.9|
| Upper arms    | 3              | 6.8 |

**Figure 1:** Bilateral earlobe keloids showed a satisfactory response to treatment after six sittings of combining FCO₂ laser and intralesional 5-FU.
The keloid etiology was surgery in 11 cases, ear piercing in 5, burn-in 4, trauma in 2, and aggressive salabrasion for tattoo removal in 2. The duration of keloids ranged from 14 to 48 months (mean 31.25 ± SD 11.6 months). A positive family was reported in three patients (12.5%). The majority of participants (79.1%) had Fitzpatrick skin type IV [Table 1].

A total of 44 keloid lesions were investigated in the 24 patients: 25 lesions in males and 19 in females. The majority of patients (83.3%) had either one or two lesions [Table 2].

Most keloids (61.3%) were located on the chest or shoulders, with others distributed on the back, ears, and upper arms [Table 3]. Itching was reported in 13 participants (54%), particularly those with presternal or earlobe keloids.

The VSS was markedly reduced after three treatment sessions, particularly in height and pliability [Figures 1–3]. The mean VSS was reduced by 65%, from 8.45 ± SD 0.93 at the baseline to 3 ± SD 1.8 one month after the end of treatment (P < 0.05). The most obvious changes were in pliability for all patients. Other changes included a reduction in lesion height in 83%, vascularity in 20.8%, and pigmentation in (16.6%) of the patients. The majority of patients (79.1%; n = 19) showed a satisfactory response to treatment, with 57.8% (n = 11) achieving an excellent results [Table 4].

A significant correlation was seen between the changes in VSS and duration of keloids: 13 out of 19 patients (68.4%) with a satisfactory response had a keloid duration of under 3 years (P < 0.05). No significant correlation was found with the age of the patients (P = 0.063) [Figure 4].

Adverse reactions such as pain, redness, and edema were transient, lasting no more than a week. Post-inflammatory hyperpigmentation and skin erosion were observed in some patients [Table 5]. No laboratory changes were recorded throughout the treatment course. The itching was resolved in patients experiencing it before treatment. Recurrences after a follow-up of 1 year were reported in four (21%) of those who responded well.

**DISCUSSION**

Keloid treatment remains a challenge in clinical practice. Keloids may lead to cosmetic and psychological embarrassment for patients. Many treatment options are available, but none are universally effective or without adverse reactions. By understanding how keloids are formed, appropriate medications can be chosen to address the causes and determine which is most effective. The pathogenesis of keloids includes the formation of excessive collagen and other extracellular matrix components. 5-FU may inhibit the synthesis of type 1 collagen, the main structural protein of scar tissue. Published data about 5-FU indicate a scheduled dose ranging from 50 to 150 mg, weekly for eight to 16 weeks. These doses are considered safe because they are small compared to intravenous chemotherapy.[18,19] Intralesional 5-FU has been tried in combination with other medications to treat keloids, with excellent results.[20]

CO2 lasers target water molecules to cause local tissue changes, including collagen remodeling, increased fibroblast growth factor, and decreased TGF-β expression. Moreover, frequent treatments with FCO2 laser have been shown to reduce keloids, primarily in terms of pliability.[15]
Evidence suggests that the use of FCO₂ laser with an adjuvant medication, as fractional laser-assisted therapy, can enhance drug delivery and potentiate the clinical efficacy of the applied drug. Given this, some research studies have described the use of topical 5-FU in combination with FCO₂ for keloids. Irradiation of the keloid lesion with the laser before the application of 5-FU can lead to a uniform distribution of the drug within the vaporized tissue columns created. A further benefit of this combination therapy is the administration of a low dose of medication to reduce undesirable adverse effects. Waibel et al. investigated laser-assisted topical 5-FU versus laser-assisted topical corticosteroid, finding no significant difference in efficacy, and determining that 5-FU had fewer adverse effects such as dermal atrophy and telangiectasia compared to the standard treatment of triamcinolone acetonide. Because the drug can diffuse more easily when used intralesionally than topically, the current study used the intralesional mode to apply 5-FU before irradiation of the keloid with FCO₂. FCO₂ laser creates coagulation and carbonization in the vaporized columns, which makes diffusion of the topical drug to the target tissue more difficult.

Compared to the recurrence rate of 21% in this study, other studies that used either FCO₂ laser or 5-FU as monotherapy for keloids found 95% and 35% recurrence, respectively, at a minimum of 3 months.

Care after treatment was required to promote rapid healing and epithelialization of damaged tissue. A daily moisturizing ointment was applied for 1 week. The patients were advised to use sunscreen on exposed treated areas. Side effects of this treatment such as pain, pruritus, redness, and local edema were transient and subsided within a few days. Other side effects such as infection, ulceration, and hyperpigmentation were not clinically significant.

Multimodal therapy was used to treat relapsing keloids including the addition of intralesional triamcinolone acetonide to the 5-FU following irradiation of the lesion with the FCO₂ laser. In addition, silicone gel was prescribed to use throughout the treatment course. It is thought that compression therapy work by reducing blood supply to the keloid tissue, resulting in hypoxia of fibroblast and increase activity of collagenase enzyme that lead to more degradation of collagen fibers.

This novel modality of laser-assisted drug delivery with intralesional 5-FU has several advantages: (1) it shortens the treatment course and reduces the number of sessions, (2) it creates a more synergistic effect on the fibrous tissue of keloids, (3) it reduces the need for large doses of the drug, and (4) it reduces the side effects, such as hyperpigmentation and ulceration.
The majority of patients exhibited a satisfactory response to combining FCO₂ laser with intralesional 5-FU for the treatment of keloids, with a low rate of recurrence. The greatest reduction was seen in pliability and height, with the least changes in vascularity and color. The modality was tolerated by the patients, and adverse reactions were transient and subsided without treatment.

**ConcluSIon**

Encouraging results were seen after six treatment sessions combining FCO₂ laser and intralesional 5-FU for the treatment of keloids. The treatment exhibited high safety and tolerability profiles.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal.

The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Tsai CH, Ogawa R. Keloid research: Current status and future directions. Scars Burn Heal 2019;5:2059513119868659.
2. Ogawa R. The most current algorithms for the treatment and prevention of hypertrophic scars and keloids. Plastic Reconstr Surg 2010;125:557-68.
3. Alster TS, Tanzi EL. Hypertrophic scars and keloids: Etiology and management. Am J Clin Dermatol 2003;4:235-43.
4. Arno AL, Gauglitz GG, Barret JP, Jeschke MG. Up-to-date approach to manage keloids and hypertrophic scars: A useful guide. Burns 2014;40:1255-66.
5. Haurani MJ, Foreman K, Yang JJ, Siddiqui A. 5-fluorouracil treatment of problematic scars. Plast Reconstr Surg 2009;123:139-48; discussion 149-51.
6. Wang XQ, Liu YK, Wang ZY, Wei Jun, Jiang YZ, Qing Chun, et al. Antimitotic drug injections and radiotherapy: A review of the effectiveness of treatment for hypertrophic scars and keloids. Int J Low Extrem Wounds 2008;7:151-9.
7. Nanda S, Reddy BS. Intralausal 5-fluorouracil as a treatment modality of keloids. Dermatol Surg 2004;30:54-6; discussion 56-7.
8. Willows BM, Ilyas M, Sharma A. Laser in the management of burn scars. Burns 2017;43:1379-89.
9. Issler-Fisher AC, Waibel JS, Donelan MB. Laser modulation of hypertrophic scars: Technique and practice. Clin Plast Surg 2017;44:757-66.
10. Hantash BM, Bedi VP, Kapadia B, Rahman Z, Jiang K, Tanner H, et al. In vivo histological evaluation of a novel ablative fractional resurfacing device. Lasers Surg Med 2007;39:96-107.
11. DeBruler DM, Blackstone BN, Baumann ME, McFarland KL, Wulff BC, Wilgus TA, et al. Inflammatory responses, matrix remodeling, and re-epithelialization after fractional CO2 laser treatment of scars. Lasers Surg Med 2017;49:675-85.
12. Ozog DM, Liu A, Chaffins ML, Ormsby AH, Fincher EF, Chippis LK, et al. Evaluation of clinical results, histological architecture, and collagen expression following treatment of mature burn scars with a fractional carbon dioxide laser. JAMA Dermatol 2013;149:50-7.
13. Qu L, Liu A, Zhou L, He C, Grossman PH, Moy RL, et al. Clinical and molecular effects on mature burn scars after treatment with a fractional CO2 laser. Lasers Surg Med 2012;44:517-24.
14. El-Zawahry BM, Sobhi RM, Bassiouny DA, Tabak SA. Ablative CO2 fractional resurfacing in treatment of thermal burn scars: An open-label controlled clinical and histopathological study. J Cosmet Dermatol 2015;14:324-31.
15. Azzam OA, Bassiouny DA, El-Hawary MS, El Maadawi ZM, Sobhi RM, El-Mesidy MS. Treatment of hypertrophic scars and keloids by fractional carbon dioxide laser: A clinical, histological, and immunohistochemical study. Lasers Med Sci 2016;31:9-18.
16. Sullivan T, Smith J, Kermod J, McIver E, Courtemanche DJ. Rating the burn scar. J Burn Care Rehabil 1990;11:256-60.
17. Baryza MJ, Baryza GA. The Vancouver Scar Scale: An administration tool and its interrater reliability. J Burn Care Rehabil 1995;16:335-8.
18. Bijlard E, Steltenpool S, Niessen FB. Intralesional 5-fluorouracil in keloid treatment: A systematic review. Acta Derm Venereol 2015;95:778-82.
19. Wang XQ, Liu YK, Qing C, Lu SL. A review of the effectiveness of antimitotic drug injections for hypertrophic scars and keloids. Ann Plast Surg 2009;63:688-92.
20. Steven P, Davison, Joseph H. Dayan, Mark W, Clemens, Smitia Sonni, Antai Wang, Amy Crane. Efficacy of intralesional 5-fluorouracil and triamcinolone in the treatment of keloids. Aesthetic Surg J 2009;29:40-6.
21. Cavalié M, Sillard L, Montaudié H, Bahadoran P, Lacour JP, Passeron T. Treatment of keloids with laser-assisted topical steroid delivery: A retrospective study of 23 cases. Dermatol Ther 2015;28:74-8.
22. Waibel JS, Wulkan AJ, Rudnick A, Daoud A. Treatment of hypertrophic scars using laser-assisted corticosteroid versus laser-assisted 5-fluorouracil delivery. Dermatol Surg 2019;45:423-30.
23. Forster B, Klein A, Szeimies RM, Maita T. Penetration enhancement of two topical 5-aminolaevulinic acid formulations for photodynamic therapy by erbium:YAG laser ablation of the stratum corneum: Continuous versus fractional ablation. Exp Dermatol 2010;19:806-12.
24. Lee WR, Shen SC, Wang KH, Hu CH, Fang JY. The effect of laser treatment on skin to enhance and control transdermal delivery of 5-fluorouracil. J Pharm Sci 2002;91:1613-26.
25. Wenande E, Olesen UH, Nielsen MM, Janfelt C, Hansen SH, Anderson RR, et al. Fractional laser-assisted topical delivery leads to enhanced, accelerated and deeper cutaneous 5-fluorouracil uptake. Expert Opin Drug Deliv 2017;14:307-17.
26. Gupta S, Kafr A. Efficacy and safety of intralesional 5-fluorouracil in the treatment of keloids. Dermatology 2002;204:130-2.
27. Norris JE. The effect of carbon dioxide laser surgery on the recurrence of keloids. Plast Reconstr Surg 1991;87:44-9; discussion 50-3.