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Effect of fractional carbon dioxide laser combined with 5-Fluorouracil injection in the treatment of hypertrophic scars and keloids

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Abstract:

Introduction: Hypertrophic scars (HTSs) and keloids are prevalent dermatological complaints caused by alternation of the normal process of wound healing.

Aim of the study: To determine the comparative effects of ablative fractional carbon dioxide laser combined with Injection of 5-fluorouracil (5FU) versus intralesional injection of (5FU) and ablative fractional CO_2 laser each as monotherapy in the treatment of hypertrophic scars and keloids.

Subjects and Methods: Thirty patients with hypertrophic scars and keloids were collected and divided into three groups. Group A: treated by intralesional 5FU plus ablative fractional carbon dioxide Laser. Group B: treated by ablative fractional CO_2 Laser as a monotherapy. Group C: treated by intralesional 5FU as a monotherapy. Results were assessed using the Vancouver Scar Scale (VSS), Observer Scar Assessment Scale and Patient Scar Assessment Scale (POSAS).

Results: Comparison between VSS before and after treatment showed a significant improvement between study groups. Post-treatment, a statistically significant difference was reported between the three groups (p = 0.0001). Post-treatment improvement was observed to favor group A followed by group B and group C.

Conclusion: 5FU injection plus Fractional CO_2 laser showed the highest improvement percentage among all groups. Fractional CO_2 laser showed acceptable results in the management of hypertrophic scars. Intralesional 5FU injection as monotherapy was accompanied by the highest incidence of complications and a decline in the evaluating scores (VSS and POSAS).

Keywords: Fractional CO_2 Laser; 5-Fluorouracil Injection; Hypertrophic Scars; Keloids.

1. Introduction

For years, keloids and hypertrophic scars have been puzzling to both patients and clinicians. The associated cosmetic disfigurement and functional disability exert a significant burden on the patient's quality of life [1]. On the other hand, the lack of substantial improvement and frequent recurrence continues to challenge clinicians. The absence of a single efficient treatment modality caused keloids to be the focus of multiple studies using a wide range of therapeutic approaches such as intralesional steroids, silicon sheets and different types of lasers [2].

The tissue is vaporized by the ablative fractional laser, leaving a milieu of microscopic ablation zones (MAZs) consisting of straight-up ablated pathways embraced by a coagulated tissue edge [3]. This fractional ablative pattern promotes collagen construction and remodeling in normal skin by regulating growth factors and cytokines [4].

5-Fluorouracil (5-FU) is a pyrimidine analogue that acts as an anticancer drug by inhibiting thymidine synthase activity and so hindering DNA and RNA synthesis. It promotes fibroblast apoptosis while avoiding necrosis, via inhibition of TGF-b1 signaling in collagen type I production, rapidly reproducing cells like fibroblasts stop growing without the structural ingredients of biosynthesis, and scar breakdown accelerates. 5-FU is also thought to inhibit type I collagen gene expression as well as tumor growth-beta effects [5].

While a universally accepted treatment strategy for hypertrophic scars has yet to be established, the use of ablative fractional laser has demonstrated promising and prolonged good clinical outcomes. Extensive evaluation has been conducted over the past decade to assess the capacity of fractional laser technology to boost transdermal drug delivery and improve the effectiveness of topical drugs [6].

This study aimed to compare the efficacy of Ablative Fractional Carbon Dioxide Laser and Intralesional 5-Fluorouracil each as a monotherapy and combined in treating Hypertrophic scars and Keloids.

2. Subjects and methods

2.1. Subjects

This study is a randomized controlled comparative and prospective study. Patients with hypertrophic scars and keloids were recruited from the outpatient clinic of the

Department of Medical Applications of Lasers at the National Institute of Laser Enhanced Sciences, Cairo University. Study protocol and written informed consent were approved by the Local Ethical Committee of Fayoum Faculty of Medicine. All patients (or legal guardians) signed a written informed consent before participation and after illustration of all study procedures and possible risks and benefits.

Inclusion criteria

We enrolled patients of any age and of both sexes who were medically fit to undergo laser procedures and 5- 5-fluorouracil injections presenting with hypertrophic scars or keloids resulting from burn scars, surgical site complications, and traumatic injuries.

Exclusion criteria

The study excluded pregnant and breastfeeding women, patients with current infections, those with connective tissue diseases, and those who had a hypersensitivity to lidocaine. Exclusion criteria for this trial included patients who had been prescribed steroids, immunosuppressive drugs, chemotherapy, or oral retinoids during the six months preceding the study. Additionally, patients with scars of significant size (covering a limb or larger), severe contracture, or those suspected of having malignancy were also excluded. In this study, those who had previously undergone laser therapy for their hypertrophic scar were removed from the analysis, as did those with scars located near the study scar.

Sample size

Sample size was estimated using SAS 9.4 statistical analysis software, the minimum required sample size was 10 per group to estimate the expected difference in post-intervention mean Vancouver scar scale between three groups 4.30±1.3 in CO2 monotherapy, 3.89±1.4 Combined CO_2 + 5-FU, and 5.67±1.4 intralesional 5FU as reported by Sabry et al. (2019), with power 80%, level of significance 5% and confidence interval 95% [7].

Table 1: Overall F Test for One-Way ANOVA.

Method	Exact
Alpha	0.05
Group Means	4.2, 3.9, 5.7
Standard Deviation	1.3, 1.4, 1.4
Nominal Power	0.8
N per Group	10
Actual Power	0.808

2.2. Methods

Study design

Thirty patients with hypertrophic scars and keloid lesions were collected and divided into 3 groups each group containing 10 patients.

Group A: Patients were treated by Intralesional 5-Fluorouracil combined with Ablative Fractional Carbon Dioxide Laser.

Group B: Patients were treated with Ablative Fractional CO_2 Laser as a monotherapy.

Group C: Patients were treated with Intralesional 5-Fluorouracil as a monotherapy.

Before therapy, all the patients were subjected to thorough history taking including age, systemic illness, duration of the scar, previous treatment trials, previous reaction to laser, and history of intake of retinoids or intralesional injections in scars.

A general examination of all patients was carried out to look for systemic illness and also included determining Fitzpatrick skin color. Local Examination of the patient's scar (site, size shape height roughness color etc..).

Laser treatment methods

a) Factional CO_2 Laser machine:

The DEKA, fractional CO_2 Laser (smart Xide DOT, Italy) was used. The device is an ablative fractional 10,600-nm CO_2 Laser with variable pulse duration (0.2-2ms), 350μm beam spot size, scanner area of 15×15 mm and penetration depth between 200 to 1,500μm. The laser settings were from clinically developed experience with prior scar and resurfacing treatments. All areas selected for inclusion had predominantly higher scars and were treated with the fractional handpiece (energy settings, Adjustments were made within the described parameters for patient comfort. The parameter used in this study was: 20 W, 800-1000μs dwell time, 2 to 3 stackings according to scar thickness, and 900μm spacing (7.4% density).

Before and after care for Fractional CO_2 Laser treatment, Lidocaine spray was applied to numb the treatment site, and ice packs were then applied to the skin for up to 30 minutes. Antibiotic ointment was prescribed for the patient till healing of the lesion was achieved. Each patient received three sessions of fractional laser treatments using the DEKA Fractional Carbon Dioxide Laser at 4-week intervals.

b) 5-Fluorouracil treatment protocol

For the intralesional injection, 1 mL of 50 mg/mL 5-FU (Utoral is available in 10 mL vial: 250 mg/5 mL: AL Hikma Pharmaceuticals, Cairo, Egypt) was mixed with 0.25 mL of local anesthesia (formed of a mixture of 20 mg/mL

lidocaine and 0.0125 mg/mL epinephrine). Weekly intralesional injections of 0.5–2 ml of 50 mg/ml 5-Flourouracil per session were administered for a max of 12 weeks.

Methods of Assessment of the Results

a) Clinical assessment

Assessments were carried out based on patient satisfaction observations and photographic records at the beginning and the end of the treatment.

Each patient was examined and photographed at baseline, at every session, and after the end of the treatment under constant conditions of distance, illumination, and exposure angle(s).

The assessments were performed by a blinded observer (a dermatology resident) before the treatments started and finished and were fulfilled via calculating the scores of both the Vancouver Scar Scale which VSS assesses four variables: vascularity, height/thickness, pliability, and pigmentation [8]; and the Patient and Observer Scar Assessment scale [9]. Also, the patients were assessed before each session and four weeks after the last session and side effects were monitored including prolonged erythema (erythema more than three days), pain (graded as mild, moderate and severe), swelling, infection, hyperpigmentation or hypopigmentation. Also, assessments were carried out based on patient satisfaction observations and photographic records at the beginning and the end of the treatment.

2.3. Statistical Methods

Statistical analysis was conducted using SPSS 22nd edition, continuous variables were presented in mean ± SD, and correlations were assessed using the Kruskul Wallis test to differentiate between groups and the Wilcoxon paired rank test, to compare paired data. Categorical variables were presented using frequencies and percentages, and correlations were made using the Chi-square (χ^2) test.

3. Results

Scars were reported to have a median length of 6.5 cm in group A, 5.5 in groups B and C with no statistically significant difference reported between groups. Duration of the scar was the longest in group B (median 24 months) followed by groups C (22 months) and finally group A (15 months) with no statistical significance reported between scar duration in the three groups as shown in (**Table 2**).

Table 2: Scar Characteristics.

Variables	Group A		Group B		Group C		*P*-value
	Median	IQR	Median	IQR	Median	IQR	
Age	17.0	11-25	35.0	30-40	29.5	19-38	0.006
Scar Length (cm)	6.5	5-8	5.5	4-7	5.5	5-7	0.60
Scar Duration (months)	15.0	8-24	24.0	18-48	22.0	14-36	0.28

Comparison between VSS before and after treatment showed a significant difference in the three groups ($p < 0.0001$). Marked improvement is reported in group A with scores 11.6 ± 0.7 versus 3.5 ± 0.7 after treatment, while groups B and C had a less profound improvement of 11.2 ± 0.9 before treatment vs. 7.6 ± 0.7 post-treatment and 11.6 ± 1.1 before treatment versus 10.2 ± 0.8 post-treatment, respectively as shown in (**Table 3**).

Table 3: Comparison of total VSS before and after treatment.

Variables	Group A		Group B		Group C		Wilcoxon rank	*P*-value
	Mean	SD	Mean	SD	Mean	SD		
Total Vancouver scale pre-treatment	11.6	0.7	11.2	0.9	11.6	1.1	-4.7	0.0001
Total Vancouver Scale post-treatment	3.5	0.7	7.6	0.7	10.2	0.8		

Improvement after completion of treatment was observed to be the highest in group A with a mean improvement of 69.9% followed by group B (32%) and group C (11.8%) ($p = 0.0001$). POSAS showed the highest improvement in group A followed by group B and C at 72.3%, 36.5%, and 8.2%, respectively ($p = 0.0001$) (**Table 4**).

Table 4: Correlations between various studied parameters in psoriasis patients.

Variables	Group A		Group B		Group C		Kruskal Wallis	*P*-value
	Mean	SD	Mean	SD	Mean	SD		
Vancouver improvement	11.6	0.7	11.2	0.9	11.6	1.1	-4.7	0.0001
POSAS improvement	3.5	0.7	7.6	0.7	10.2	0.8		

Improvement of VSS was significantly correlated to age (p = 0.027), while there were no such correlations with scar length or scar duration, as shown in **Table 5**.

Table 5: Correlation between scores and scar characters in VSS.

Variable	Vancouver improvement score	*P*-value
Age	-0.404	0.027
Scar length	0.091	0.63
Scar duration	-0.166	0.37

Age was significantly correlated to improvement in POSAS (p = 0.035), while scar length and duration were not significantly correlated to POSAS improvement (**Table 6**).

Table 6: Correlation between scores and scar characters in POSAS.

Variable	POSAS improvement score	*P*-value
Age	-0.386	0.035*
Scar length	-0.002	0.99
Scar duration	-0.242	0.19

Skin pigmentation was improved only in group A (6.4%), while in groups B and C there was a worsening of skin pigmentation (-8.7% and -13.2%, respectively). There was statistically significant difference with p value 0.028, as shown in. Skin vascularity was significantly improved in group A with 72%, while in group B it was 23.8%; however, in group C, there was a worsening of vascularity with -28.4%. There was statistically significant difference between groups favoring group A on other groups, with p value 0.0001, as shown in. Skin pliability was markedly improved in group A, reaching an 85% improvement from the baseline score, while groups B and C showed 42.8% improvement and 12.8% worsening. Comparison between groups showed significant difference in improvement of skin pliability (p = 0.0001), as shown in. Skin height showed significant improvement in group A with 71.3%, while in group B there was a lesser improvement of 41.7%. On the other hand, in

group C there was a worsening of skin height with 11.2%. This led to a significant difference (p = 0.0001), as shown in **Table 7**.

Table 7: Percentage improvement in Vancouver score components.

Variables	Group A		Group B		Group C		Kruskal Wallis	*P*-value
	Mean	SD	Mean	SD	Mean	SD		
VSS pigmentation	6.4%	11.2%	-8.7%	9.5%	-13.2%	28.6%	7.12	0.028
VSS vascularity	72.4%	6.4%	23.8%	13.3%	-28.4%	22.8%	25.7	0.0001
VSS pliability	85.0%	1.2%	42.8%	14.5%	-12.8%	36.3%	25.9	0.0001
VSS height	71.3%	6.5%	41.7%	13.7%	-11.2%	12.7%	25.3	0.0001

POSAS pain component was significantly improved in group A versus group B; however, it was worse in group C (p = 0.0001), as shown in. Itching was significantly improved in groups A and B with 83.4% and 42.1%, respectively, while it was worse in group C (18.0%) (p = 0.0001). The color of the skin post-treatment was significantly improved in group A (68.8%), in group B (30.9%), and worsened in group C (-40.4%). This showed a significant difference favoring group A intervention (p = 0.0001), as shown in. There was improvement in skin thickness mainly in group A, followed by group C, and then group B with 75.4%, 44.44%, and 39.1%, respectively. difference was reported with p value 0.0001, as shown in. Regarding skin stiffness, group A (72.2%) showed significant improvement versus groups B and C (43.0%, 26.5%) (p = 0.0001). Skin irregularity was significantly improved in group A compared to the other two groups (p = 0.0001) (**Table 8**).

Table 8: Percentage improvement in each variable of POSAS.

Variables	Group A		Group B		Group C		Kruskal Wallis	*P*-value
	Mean	SD	Mean	SD	Mean	SD		
Improvement Painful	77.3%	5.5%	36.6%	7.1%	-10.2%	12.7%	26.1	0.0001
Improvement Itching	83.4%	2.1%	42.1%	9.4%	-18.0%	3.3%	26.0	0.0001
Improvement Color	68.8%	7.6%	30.9%	9.6%	-40.4%	37.8%	26.04	0.0001

Improvement Stiffness	72.2%	3.6%	43.0%	4.6%	26.5%	2.3%	26.1	0.0001
Improvement Thickness	75.4%	6.8 %	39.1%	2.6%	44.4%	7.3%	21.45	0.000 1
Improvement Irregularity	65.3%	5.9 %	45.3%	7.6%	38.1%	11.8%	20.05	0.000 1

Moderate pain was highly experienced in group C (100%), to a lesser extent in group B (70%), and the least in group A (30%) (p = 0.004). Infections were reported only in Group C, representing 44.4% of patients who experienced scar infections during the treatment course. There was a statistically significant difference in the incidence of scar infection between the three groups (p = 0.006). All cases of group C reported scar swelling, which was more prevalent than group A, with only 40% of the included patients suffering from scar swelling. While in group B, there was no reported scar swelling during the treatment course. This difference was statistically significant (p = 0.0001). Erythema was significantly higher in groups A and B (100%), while in group C it only represented 20% of included patients with a significant difference (p = 0.0001), as shown in **Table 9**.

Table 8: Incidence of complications.

Variables		**Group A**		**Group B**		**Group C**		χ^2	***P*-value**
		N	**%**	**N**	**%**	**N**	**%**		
Pain	No pain	0	0%	0	0%	0	0%	11.1	0.004
	Mild pain	7	70%	3	30%	0	0%		
	Moderate pain	3	30%	7	70%	10	100%		
Infection	No	10	100%	10	100%	5	55.6%	10.3	0.006
	Yes	0	0%	0	0%	4	44.4%		
Swelling	No	6	60%	10	100%	0	0%	20.35	0.0001
	Yes	4	40%	0	0%	10	100%		
Erythema	No	0	0%	0	0%	8	80%	21.8	0.0001
	Yes	10	100%	10	100%	2	20%		

Figure 1: Group A: Fractional Carbon Dioxide Laser and 5- Fluorouracil injection. A hypertrophic traumatic scar in the chin with marked improvement in vascularity, height, pliability and pigmentation after completion of treatment plan (Case 1).

Figure 2: Group B: Fractional Carbon Dioxide Laser only. A cut wound scar in the arm of a teenager showing marked improvement of skin pigmentation and pliability at the end of treatment sessions (Case 9).

Figure 3: Group C: 5- Fluorouracil injection. A child showing no improvement in VSS in response to treatment of a facial scar caused by a sharp object (Case 18).

4. Discussion

In our study, the duration of the scar was the longest in group B (median 24 months), followed by group C (22 months), and finally group A (15 months), with no statistical significance reported between scar duration in the three groups. However, this was much longer than reported in other studies conducted on a comparable cohort, with the mean duration of the lesions being 18.6 and 18.8 months, respectively [7, 10]. In addition to another study on the histopathological changes of the scar tissue after applications of fractional CO2 lasers, the mean duration of the scar was 8.1 months [11].

Comparison between VSS before and after treatment showed a significant difference in the three groups with a p value of 0.0001. Marked improvement is reported in group A with scores of 11.6 ± 0.7 versus 3.5 ± 0.7 after treatment, while groups B and C had a less profound improvement of 11.2 ± 0.9 before treatment vs. 7.6 ± 0.7 post-treatment and 11.6 ± 1.1 before treatment versus 10.2 ± 0.8 post-treatment. This was confirmed by Shah et al. (2016), who reported that the group who received combined 5FU plus fractional leaser was superior to other arms with a significant improvement in the total VSS after completion of the treatment course [5].

While POSAS showed the highest improvement in group A (72.3%), followed by group B (36.5%), and then group C (8.2%), there was a statistically significant difference. This was confirmed by Lee et al. (2018), who reported that patients who underwent 5FU plus fractional leaser in a periocular scar certified that all components of POSAS were improved after completion of therapy [12].

Our results were not in accordance with the early trials done with 5FU intralesional injection in hypertrophic scars, as they reported very high improvement, reaching 80% in all included patients [13, 14].

In the present study, improvement of VSS was significantly correlated to age, while there were no such correlations with scar length or scar duration. In addition, age was significantly correlated to improvement in POSAS, while scar length and duration were not significantly correlated to POSAS improvement, which agrees with Azzam et al. (2016), who concluded that young patients are better responders to laser resurfacing, probably because of the cytokines and growth factors involved in early wound maturation [15]. Our study disagreed with Tawfik et al. (2019), who stated that age, sex, site, skin type, length, and

duration of the scar didn't significantly affect the percentage of improvement [10].

In the present work, skin vascularity was significantly improved in group A with 72%, while in group B it was 23.8%; however, in group C, there was a worsening of vascularity with -28.4%. There was a statistically significant difference between groups favoring group A over other groups, which agrees with Shah et al. (2016) [5]. On the contrary, this was disapproved by another study, which concluded that all treatment arms had improved skin vascularity in VSS [7].

Our results showed that skin pigmentation was improved only in group A (6.4%), while in groups B and C there was a worsening of skin pigmentation (-8.7% and -13.2%, respectively). There was a statistically significant difference. On the other hand, this was rejected by other studies, which concluded that skin pigmentation was not significantly improved in the three included groups [7, 10].

Our study showed that skin pliability was markedly improved in group A, reaching 85% improvement from the baseline score, while groups B and C showed 42.8% improvement and 12.8% worsening. Comparisons between groups showed a significant difference in the improvement of skin pliability. This was actually in agreement with the other two studies, which stated that the VSS total score was markedly improved in the 5FU arm, and this was mainly reflecting the improvement in skin pliability [7, 10].

Using the POSAS score, the pain component was significantly improved in group A versus group B; however, it worsened in group C. Itching was significantly improved in groups A and B with 83.4% and 42.1%, respectively, while it was worse in group C (18.0%). Our results were consistent with those of Sabry et al. (2019) and Lee et al. (2018), who reported pain control in all studied arms; however, the 5FU group achieved the highest control of pain [7, 12]. However, it was in contrast with early studies, which stated that intra-lesioned injection of 5FU showed only mild pain and pruritus at the site of injection, which was managed with analgesics [16].

Regarding the complications after treatment completion in our study, erythema was significantly higher in groups A and B, and pain was highly experienced in group C (100%). Infections occurred significantly higher in group C. In addition, all cases of group C reported scar swelling, which was more prevalent than group A. Only 40% of the included patients suffered from scar swelling; this difference was statistically significant. This was comparable to the studies that used intra-lesioned injections of

5FU, as patients reported scar infection, swelling, and superficial ulcerations. However, in these studies, all complications were easily managed and didn't yield any long-term morbidity [13, 17]. On the other hand, a study performed by Lee et al. (2016) showed that hyperpigmentation was the commonest side effect post-treatment, which was in contrast to our results [18].

Conclusion

5FU injection along with fractional CO_2 laser showed the highest improvement percentage among all groups. Fractional CO_2 laser showed acceptable results in the management of hypertrophic scars; however, it was inferior to the combination with the 5FU arm. Intralesional 5FU injection as monotherapy was accompanied by the highest incidence of complications and a decline in the evaluating scores (VSS and POSAS).

Ethical consideration and patient consent: The study was approved by the Faculty of Medicine, Fayoum University Research Ethical Committee (Approval no., M468 - 12/1/2020).

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Conflicts of Interest: All authors declare they have no conflicts of interest.

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