Assessment of the Effectiveness of Steroid Injection versus 5-Fluorouracil Injection Following Fractional Ablative Erbium Yttrium Aluminum Garnet Laser in Hypertrophic Scars

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Abstract

Background*: Hypertrophic scar (HTS) is a significant dermatological pathology resulting from disrupted healing and has multiple cosmetic and psychological impact. Still there is no gold standard therapy. *Aim*: The current study aimed to compare between two treatment options: intralesional steroids versus intralesional 5-fluorouracil injections following Erbium YAG fractional laser therapy. *Patients and Methods:* A total of 30 patients with HTS of any size lasting from 6 months to 1 year have been included into the study during the period from March 2020 to August 2021. Scar severity was done using the Vancouver scar scale (VSS). All patients were first treated with fractional ablative 2,940 nm Erbium YAG laser. After Laser session the lesion was divided into two halves. First half was injected with intralesional triamcinolone acitonide (TAC) (Epirelefan vial, Eipico, Egypt) (40 mg/1ml). The other side was injected with intralesional 5-fluorouracil (Utoral 250 mg/5ml ampules, EMIC United Pharmaceuticals) (0.1ml/2.5 cm). Patients were evaluated for change in VSS, patient satisfaction and recurrence rate. *Results:* Patients treated with 5-FU have lower VSS at post treatment assessment (3.37 ± 2.72) versus patients treated with steroid (5.03 ± 1.16). Recurrence rate was significantly higher among steroid-treated patients (46.7%) versus 16.7% among 5-FU treated patients (p-value = 0.01. *Conclusion:* Both intralesional 5-FU and steroid are effective when administered following treatment with fractional ablative 2,940 nm Erbium YAG laser. However, 5-FU revealed higher efficacy compared to intralesional steroid injection with lower significantly lower rate of recurrence.

Keywords: scar, intralesional injection, glucocorticoid, laser ablation.

Introduction

Skin damage can result from various causes, including physical trauma, skin punctures, herpes infections, burns, and surgical incisions. Deep wounds often lead to hypertrophic scars (HTS) [1].

Hypertrophic scars arise from an excessively vigorous healing response to skin injury. This pathological process is primarily characterized by a disruption in the delicate balance between the breakdown and formation of extracellular matrix (ECM) proteins produced by fibroblasts, particularly due to excessive collagen production [2].

Proper management of hypertrophic scars is essential, not only because of the cosmetic disfigurement they cause but also due to their potential psychological impact [2]. A variety of treatment options are available,

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including surgical excision, topical therapies, intralesional injections, and laser therapy. However, a definitive gold standard for HTS management has not yet been established [3].

Corticosteroids have long been used in the management of hypertrophic scars, either topically or via intralesional injection. Topical corticosteroids may cause adverse effects such as dermal atrophy, telangiectasia, and hypopigmentation [4], while intralesional injections are often associated with painful repeated procedures and variable efficacy [2].

An alternative treatment option is 5-fluorouracil (5-FU), a fluorinated pyrimidine analog that acts as an antimetabolite by inhibiting thymidylate synthase and disrupting RNA synthesis. It is used for its ability to suppress fibroblast proliferation and reduce collagen synthesis [5].

The concept of fractional photothermolysis using fractional lasers has gained popularity, especially with the introduction of ablative wavelengths generated by erbium: yttrium aluminum garnet (YAG) (2,940 nm) and carbon dioxide (CO_2) (10,600 nm) lasers. The erbium: YAG laser is recognized as one of the pioneering devices capable of effectively and safely ablating reticular dermal tissue for the purpose of resurfacing photodamaged skin [6].

Given the absence of an established gold standard for HTS treatment, the present study aims to compare two treatment modalities: intralesional corticosteroids versus intralesional 5-fluorouracil injections, both administered following erbium: YAG fractional laser therapy.

Patients and methods:

After obtaining approval from the Ethics Committee of the Faculty of Medicine, Suez Canal University, we conducted an interventional randomized clinical trial to evaluate the effect of laser treatment on hypertrophic scars (HTSs) followed by either intralesional corticosteroid injection or intralesional 5-fluorouracil injection. The study included 30 patients with hypertrophic scars who attended the Dermatology Outpatient Clinic at Suez Canal University Hospital between March 2020 and August 2021.

Eligible participants were adults over 18 years of age, of either gender, presenting with hypertrophic scars of any size that had persisted for 6 months to 1 year, and with skin types II–V according to the Fitzpatrick scale [7]. Pregnant or lactating women were excluded. Immunocompromised individuals such as those receiving long-term corticosteroid therapy, diagnosed with malignancies, or with uncontrolled diabetes were also excluded. In addition, patients who had received any scar treatment within the 6 months preceding the start of the study were not included.

Pre-intervention Patients evaluation:

Patients underwent a comprehensive evaluation that included medical history, general examination, and dermatological assessment to identify any systemic diseases or other dermatological conditions. Scar tissue was carefully assessed, with documentation of the site, size, pattern, and distribution of each lesion.

Assessment of scar tissue was performed carefully with reporting site, size, pattern and distribution of each individual lesion. Assessment of scar severity was done using the Vancouver scar scale (VSS) [8]. It assesses 4 subjective variables: vascularity (3 point as normal =0 and purple= 3), height/thickness (3points as flat =0 and mor than 5 mm=3), pliability (5point as normal =0 and contracture =5), and pigmentation (2piont as normal =0 and hyperpigmented =2) within a possible range of 0 - 13 for the total score.

Intervention:

An anesthetic cream containing 2.5% lidocaine and 2.5% prilocaine (Pridocaine Cream, Glopal Napi, and Egypt) was administered under occlusion for 30 minutes before the procedure. Afterward, the complete lesion was treated with a fractional ablative 2,940 nm Erbium YAG laser (Fotona Dynamis SP, Ljubljana, Slovenia).

The laser parameters were set as follows: a fluency of 10 J/cm², an ablation depth ranging from 50 to 200 µm, handpiece model PS01, a spot size of 7 mm in diameter, operation in short pulse (SP) duration mode, a density level between 2 and 3, a frequency of 4 to 5 Hz, and targeting 10% coverage area. A consistent overlap of 30-40% between spots was ensured. Two passes were performed consecutively. In the initial pass, the laser spots were applied pulse by pulse in a vertical orientation, while in the second pass, the application was made in a horizontal direction. The laser handpiece was maintained perpendicular to the area being treated. No simultaneous use of an epidermal device was performed during the procedure. An ice pack was applied for 10 minutes following the treatment.

Following the laser treatment, the lesion was separated into two sections. The first section received an injection of intralesional triamcinolone acetonide (Epirelefan vial, Eipico, Egypt) (40 mg/1ml).

The other side was injected with intralesional 5-fluorouracil (Utoral 250 mg/5ml ampules, EMIC United Pharmaceuticals) (0.1ml/2.5 cm).

Uniform injection methods were utilized with consistent syringe size (3mL), needle size (27 Gauge), Luer Lock, and pharmaceutical drug brands. The volume of the injection was determined by the size of each patient's HTS.

A total of four treatment sessions were administered: each spaced four weeks apart. Patients were monitored for 12 weeks following the final session. After each treatment, they were instructed to apply fusidic acid 2% cream for five days to manage any skin irritation.

The status of hypertrophic scars before treatment initiation and throughout the follow-up period was documented photographically. Each treated site was evaluated using the Vancouver Scar Scale (VSS) by an independent dermatologist based on the photographs.

Patient satisfaction with the treatment outcome was self-assessed using four response options: not satisfied, slightly satisfied, moderately satisfied, or extremely satisfied.

For statistical analysis, data were processed and evaluated using the SPSS statistical software Version 20. Quantitative data were presented as mean ± SD, while qualitative data were represented as numbers and percentages. Paired t-tests were applied to quantitative variables. Test for marginal homogeneity was employed for qualitative variables. A p-value of <0.05 was deemed statistically significant.

Results:

As presented in **table 1**, the age of examined patients ranged from 18-63 years with a mean age of 31.87 and standard deviation (SD) ± 11.18, about 56.7% of them were females and 43.3% were males. The lesions of the examined cases were of average size 3.93 ± 1.31 cm, about 56.7% of them had lesions >3 cm. The most reported pattern was: linear (76.6%), both rounded and oval represented only (10%), and triangular only once (3.3%). The most reported skin type was: type III (53.3%), then type IV (23.3%), type II (16.7%) and type V (6.7%) respectively. The most reported factor was: burn (60%), then trauma (26.7%), operation (10%) and Post herpetic (3.3%) respectively. The duration of the studied lesions was of average 0.75 ± 0.16 years.

Table 1: Personal and baseline scar characteristics among the studied patients:

		Number	Percentage
Sex	Male	13	43.3%
	Female	17	56.7%
Age	≤ 30 years	15	50%
	> 30 years	15	50%
Family history of HTS		10	33.3%
Scar size	≤ 3 cm	13	43.3%
	> 3 cm	17	56.7%
Scar pattern	Linear	23	76.7%
	Rounded	3	10%
	Triangular	1	3.3%
	Oval	3	10%
Skin type (Fitzpatrick scale)	II	5	16.7%
	III	16	53.3%
	IV	7	23.3%
	V	2	6.7%
Underlying scar cause	Surgery	3	10%
	Burn	18	60%
	Trauma	8	26.7%
	Post herpetic	1	3.3%
Duration of scar (years)	Mean ± SD	0.75 ± 0.16	
	Range	0.5 – 1	

HTS: Hypertrophic scar

Half of the lesions (53.3%) after 5-FU injection turned pink than before the treatment and this change is statistically significant (P-value <0.05). Half lesions (50%) after steroid intralesional injection turned normal than before the treatment and this change is statistically significant (P-value <0.05). The comparison between the effect of steroid intralesional injection and the effect of 5-FU injection on vascularity revealed that half of the lesions after 5-FU turned pink (53.3%) and red (26.7%) while after steroid turned normal (50%) and pink (40%), respectively, and these differences were statistically significant (P-value

<0.05). Half of lesions (50%) after 5-fluorouracil injection turned normal than before the treatment and this change is statistically significant (P-value <0.05). Most lesions (76.7%) after steroid intralesional injection turned mixed than before the treatment and this change is statistically significant (P-value <0.05). Half of the lesions after 5-fluorouracil turned normal (50%) and less than half turned mixed (40%) while after steroid turned mixed (76.7%) and hyper (20%) respectively, and these differences were statistically significant (P-value <0.05). Half of the lesions (50%) after 5-FU injection turned normal than before the treatment and this change is statistically significant (P-value <0.05). Most lesions (70%) after steroid intralesional injection turned supple than before the treatment and this change is statistically significant (P-value <0.05). The comparison between the effect of steroid intralesional injection versus the effect of 5-FU intralesional injection after Er:YAG laser treatment according to Pliability was illustrated. Half of the lesions after 5-FU turned normal (50%) and supple (36.7%) while after steroid turned supple (70%) and Yielding (26.7%) respectively, and these differences were statistically significant (P-value <0.05). As regarding the height of the lesions, more than half of the lesions (60%) after 5-FU injection turned flat than before the treatment and this change is statistically significant (P-value <0.05). Most lesions (80%) after steroid intralesional injection turned <2mm than before the treatment and this change is statistically significant (P-value <0.05). Most lesions after 5-FU turned flat (60%) and <2mm (33.3%) while after steroid turned <2mm (80%) and 2-5mm (13.3%) respectively, and these differences were statistically significant (P-value <0.05). The studied lesions reduced in score after both 5-FU injection and steroid intralesional injection, and this reduction is statistically significant (P-value <0.05). VSS total score after 5-FU intralesional injection was less than the score after steroid intralesional injection and this offered faster response and better improvement in case of 5-FU intralesional injection after Er:YAG laser, than in case of steroid intralesional injection after Er:YAG laser **(Table 2)**.

Slightly less than half of the studied patients became extremely satisfied after 5-FU (40%) versus only 3.3% of the steroid group and this difference was statistically significant (P-value <0.05), as presented in **table 3.** Most of the cases showed markedly higher recurrence rate after steroid (46.7%) than that after 5-FU (16.7%), and this difference was statistically significant (P-value <0.05).

Table 2: Comparison between the two treatment arms (steroid and 5-FU) regarding treatment outcome:

Characteristics		Before treatment		After YAG laser and 5-FU		After YAG laser and steroid	
		No	%	No	%	No	%
Vascularity	Normal	0	0%	5	16.7%	15	50%
	Pink	7	23.3%	16	53.3%	12	40%
	Red	15	50%	8	26.7%	3	10%
	Purple	8	26.7%	1	3.3%	0	0%
	Significance	P1< 0.001*		P2< 0.001*		P3< 0.001*	
Pigmentation	Normal	0	0%	15	50%	1	3.3%
	Hypopigmentation	0	0%	0	0%	0	0%
	Mixed	6	20%	12	40%	23	76.7%
	Hyperpigmentation	24	80%	3	10%	6	20%
	Significance	P1< 0.001*		P2< 0.001*		P3< 0.001*	
Pliability	Normal	0	0%	15	50%	1	3.3%
	Supple	0	0%	11	36.7%	21	70%
	Yielding	9	30%	4	13.3%	8	26.7%
	Firm	19	63.3%	0	0%	0	0%
	Banding	1	3.3%	0	0%	0	0%
	Contracture	1	3.3%	0	0%	0	0%
	Significance	P1< 0.001*		P2< 0.001*		P3< 0.001*	
Height	Flat	0	0%	18	60%	2	6.7%
	< 2 mm	0	0%	10	33.3%	24	80%
	2 – 5 mm	24	80%	2	6.7%	4	13.3%
	> 5 mm	6	20%	0	0%	0	0%
	Significance	P1< 0.001*		P2< 0.001*		P3< 0.001*	
Total VSS score	Mean ± SD	9.83 ± 1.26		3.37 ± 2.72		5.03 ± 1.16	
	Median (IQR)	10 (9 – 11)		3 (1 – 5)		5 (4 – 6)	
	Significance	P1< 0.001**		P2< 0.001**		P3< 0.001**	

p_1: p value for comparing between before and after 5-FU & laser
p_2: p value for comparing between before and after steroid & laser
p_3: p value for comparing between after 5fu & laser and after steroid & laser
**p-value for marginal Homogeneity Test **p-value for Wilcoxon signed ranks test*
Statistically significant if p-value < 0.05
5-FU: 5-Fluorouracil, IQR: interquartile range, SD: Standard deviation, VSS: Vancouver scar scale, YAG: Yttrium Aluminum Garnet

Table 3: Patient satisfaction and rate of recurrence among the two treatment arms (steroid and 5-FU):

Characteristics		After YAG laser and 5-FU		After YAG laser and steroid		p-value
		No	%	No	%	
Patient satisfaction	Not satisfied	3	10%	2	6.7%	0.001*
	Little satisfied	4	13.3%	13	43.3%	
	Moderately satisfied	11	36.7%	14	46.7%	
	Extremely satisfied	12	40%	1	3.3%	
Recurrence rate	Negative recurrence	25	83.3%	16	53.3%	0.01**
	Positive recurrence	5	16.7%	14	46.7%	

*p-value for marginal Homogeneity Test **p-value for McNemar test
Statistically significant if p-value < 0.05

Figure 1 showed a photographic evaluation of HTS before treatment (A), after 2 sessions of treatment (B) and after the last session and 12 weeks follow up (C).

Figure 2 showed a photographic evaluation of HTS before treatment (A), after 2 sessions of treatment (B) and after the last session and 12 weeks follow up (C).

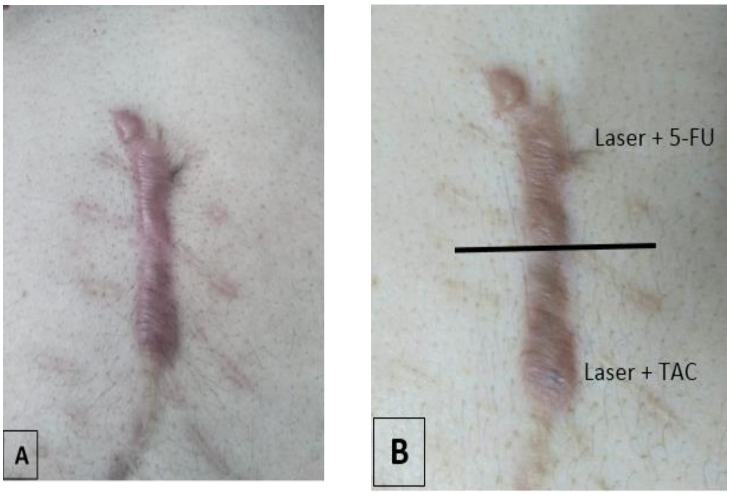

Figure 1: Abdominal HTS case before and after treatment modalities:
TAC: triamcinolone acitonide, 5-FU: 5-Fluorouracil

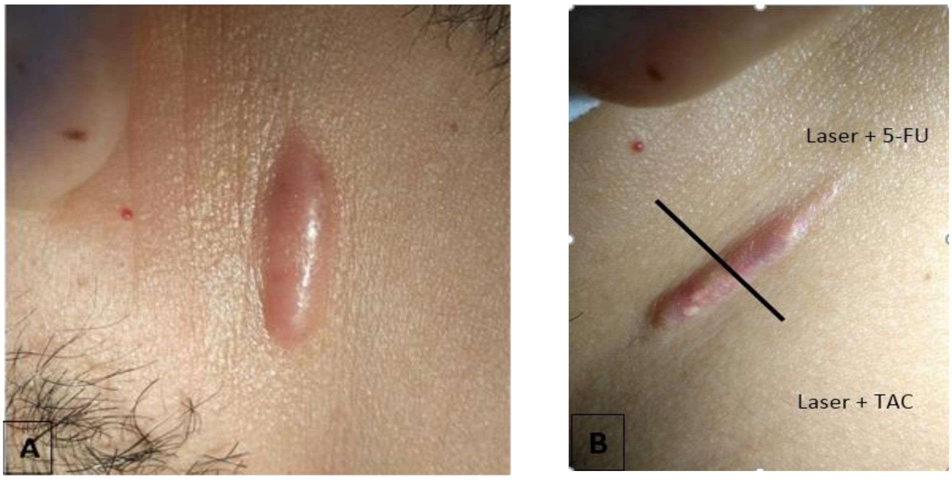

Figure 2: Neck HTS case before and after treatment modalities:
TAC: triamcinolone acitonide, 5-FU: 5-Fluorouracil

Discussion:

The current study was designed as a clinical trial to compare between intralesional steroid and 5-FU following Erbium YAG fractional laser therapy.

We have included a total of 30 patients with HTS. All patients were first treated with fractional ablative 2,940 nm Erbium YAG laser. After Laser session the lesion was divided into two halves. First half was injected with intralesional triamcinolone acitonide (Epirelefan vial, Eipico, Egypt) (40 mg/1ml). The other side was injected with intralesional 5-fluorouracil (Utoral 250 mg/5ml ampules, EMIC United Pharmaceuticals) (0.1ml/2.5 cm).

In the present study the most common precipitating factor of HTS formation was post burn and this was shown in 18 cases (60%). Furthermore, post traumatic HTSs were 8 (26.7%), post -operative were 3 (10%), and post herpetic was only one (3.3%). On contrary to Abd El-Dayem et al. (9) who demonstrated that trauma was the most common cause of keloid formation which was observed in 50% of their cases. Also Tawfik et al. (10) mentioned that the most common cause was post-traumatic wound (66.6%)

In the current study, intralesional injection of 5-FU after Er:YAG laser treatment resulted in a significant improvement better than intralesional steroid in terms of pigmentation, pliability, and height more than TAC following laser while steroid showed better improvement only in vascularity of the wound. Similarly, Kabel et al., (11) has shown improvement of pliability and height with intralesional 5-FU.

Also Tawfik and colleagues (10) have concluded a significant improvement of scar height and pliability with significant decrease of total VSS with intralesional injection of 5-FU.

In the present comparative study, VSS total score after 5-FU intralesional injection showed less score than that after steroid intralesional injection following Er:YAG laser on both sides of lesions, and this offered faster response and better improvement in case of 5-FU intralesional injection after Er:YAG laser, than in case of steroid intralesional injection after Er:YAG laser.

Supporting our current findings, Waibel and colleagues (12) as well as Darougheh et al., (13) have concluded that intralesional 5-FU is superior to intralesional steroid in the treatment of HTS particularly in terms of treatment side effects.

We have found that patients treated with intralesional steroid have significantly higher recurrence rate compared to patients treated with intralesional 5-FU. Consistently Khalid et al., (14) have reported a lower recurrence rate with 5-FU therapy.

The main limitations of the current study are the small sample size, the lack of histopathological evaluation and the relatively short period of follow up.

Based on the current study, we can conclude that both intralesional 5-FU and steroid are effective when administered following treatment with fractional ablative 2,940 nm Erbium YAG laser. However, 5-FU revealed higher efficacy compared to intralesional steroid injection with lower significantly lower rate of recurrence.

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