Fractional Microneedling Radiofrequency Versus Intralesional Steroid Injection with and Without Microneedling on Tissue Levels of PDGF And CTGF In Hypertrophic Scars: A Randomized Comparative Clinical Trial.

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Abstract

Background: Hypertrophic scarring is a fibroproliferative disorder that can cause severe functional and cosmetic deformities, and unfortunately is still lacking a reliable treatment method. Objective: To evaluate and compare the efficacy and safety of fractional microneedling radiofrequency (FMR) versus intralesional corticosteroid injection (ILCS) followed or not by microneedling in the treatment of hypertrophic scars and their implication on platelet derived growth factor (PDGF) and connective tissue growth factor (CTGF) tissue levels. Methods: One side of the hypertrophic scar of the thirty enrolled patients, was randomly treated with FMR, and the other half was treated by ILCS injection alone or followed by microneedling for 5 sessions with 1-month intervals. Evaluation of response was done by clinical assessment, patient and observer scar assessment scale, and biochemical PCR measurement of tissue levels of both PDGF and CTGF at baseline and 1 month after the last session. Results: Both therapeutic modalities yielded clinical and biochemical statistically significant improvements of HTSs ($p<0.05$). By comparing both modalities, there was no clinical statistical significance, however, ILCS showed significant decrease in biochemical parameters. Conclusion: FMR, ILCS and microneedling are all effective in the treatment of hypertrophic scars. FMR is a safe option for treatment of HTSs in dark skinned patients, with low downtime and rapid healing. ClinicalTrials.govID: NCT04389619

Keywords: Hypertrophic scars, Fractional Microneeding Radiofrequency (FMR), intralesional steroid injection (ILCS), microneedling.

1. Introduction

Hypertrophic scars result from abnormal cutaneous wound healing processes due to hyperproliferation of the dermal fibroblasts with excessive collagen deposition, and persistent inflammation and fibrosis [1]. Hypertrophic scars can cause severe functional and cosmetic deformities, discomfort, pain, itching, may affect the range of joint movement and quality of life, and unfortunately is still lacking a reliable treatment method [2].

Intralesional steroid injection (ILCS) is considered the first line of treatment of hypertrophic scars and insoluble triamcinolone acetonide is the most used type, however pain and atrophy are common side effects [3]. Microneedling therapy is a minimally invasive non-surgical and non-ablative procedure to create controlled skin injury [4]. Micro punctures lead to minimal superficial bleeding and set up a wound healing cascade with release of various growth factors [5].

Fractional Microneedling Radiofrequency (FMR) is a novel radiofrequency technique that uses microneedles to deliver energy to the deep dermis at the point of penetration without destruction of the epidermis. The amalgamation of microneedling with radiofrequency has expanded the applications of this technology to include various dermatological conditions including scar treatment, hyperhidrosis, skin tightening and rejuvenation [5, 6].

Various growth factors and pathways are implicated in scar formation. Platelet derived growth factor (PDGF) is a disulfide-linked dimeric protein, that contributes to tissue remodeling during wound healing by upregulating matrix metalloproteinases,

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and production of the collagenase proenzyme by skin fibroblasts [7].

Another target protein directly involved in extracellular matrix synthesis is connective tissue growth factor (CTGF). In addition to its direct fibrogenic effect, CTGF can exacerbate transforming growth factor β (TGF-β)-induced fibrosis by activating SMAD signaling through facilitating the binding of TGF-β to its receptor, therefore it is recognized as a TGF-β downstream modulator protein in fibroblasts [8, 9].

Therefore, the aim of the current study was to evaluate and compare the effectiveness and side effects of FMR versus ILCS followed or not by microneedling in the treatment of hypertrophic scars and their implication on PDGF and CTGF tissue levels.

2. Materials and methods

Patients and Ethical Considerations

The current study included 30 male and female Egyptian patients with hypertrophic scars. Patients were recruited from the outpatient clinic of the Dermatology Department of Cairo University between January 2020 and June 2021. Both male and female patients were included if they were older than 16 years of age and had two separate scars, each of at least 3 cm long or a large sized scar of at least 10 cm long. Patients were excluded if they were pregnant, lactating, had bleeding disorders, had received any form of treatment for scars or isotretinoin therapy during the last six months of the beginning of the study. This study was approved by the Dermatology Department Research Ethics Committee of the Faculty of Medicine, Cairo University (ClinicalTrials.govID: NCT04389619). All patients provided written informed consent before participation in this study to undergo biopsy, photography, and treatment.

History and Examination

A thorough history, including name, age, occupation, systemic diseases, cause of the scar, scar duration, previous treatment, and the use of retinoid or steroid injection was obtained from all patients included in the study. Examination included determining the Fitzpatrick scale skin color of patients, site, and extent of the hypertrophic scars to be treated.

Treatment

This is a randomized, controlled, comparative study. Each patient received 5 treatment sessions at 4-week intervals. In every patient, each one of the two scars, or each side of a large scar was randomly assigned to treatment either by FMR (area A) (all 30 patients) or ILCS injection alone (in 15 patients) or IL CS combined with MN (in 15 patients) (area B). Lesions were randomly assigned to treatment. Randomization was done using the sealed envelope method.

Area A: Fractional Microneedling Radiofrequency:

1. FMR Bipolar VIVACE device was used in the current study using cartridges with 36 non-insulated microneedles. Parameters used: were power of 6 volts, exposure time of 800 milliseconds, depth of 3.5 mm, and frequency of 2 Hertz.
2. The handpiece was applied firmly and perpendicular to the treatment area. The footswitch was then pressed to deliver RF energy. The handpiece was then completely released from the skin rather than sliding the needles to avoid abrasions. The handpiece was moved to the adjacent area with an overlap of approximately 50%. One to 2 additional pulses were applied at the same site (stacking).
3. Minor pinpoint bleeding points were commonly encountered.

Area B:

Area B scars were randomly subgrouped into two equal groups, one group (B1) treated with only ILCS injection, and the other group (B2) treated with ILCS injection and followed by microneedling.

Intralesional corticosteroids injection (ILCS): Triamcinolone acetonide was diluted with saline in concentration 1:2 (20 mg/ml) and injected using an insulin syringe along the scar.

Microneedling

1. A handheld motorized microneedling device was used. Sterile disposable needle cartridges (30 gauge / 36 needle array) were used at needle depths of 2mm at a speed fixed at 90-95 times/sec.
2. Normal saline was applied on the scars to facilitate gliding action of the microneedling device during treatment. Gentle traction of the skin with one hand while simultaneous application of the microneedling tip perpendicular to the scar(s) with the other hand assisted with the smooth delivery of microneedles into the skin were applied.
3. A combination of horizontal, vertical, and oblique device passes over the treatment areas were delivered until uniform pinpoint bleeding was observed (4 to 10 passes).

Clinical Assessment

A baseline assessment was conducted before treatment, followed by an additional assessment 4 weeks after the final treatment session. The assessments were performed by a certified dermatologist who was blinded to the treatment parameters, and the Patient and Observer Scar Assessment Scale (POSAS) was used. The side effects related to treatment were evaluated after each treatment session and during the follow-up period. Digital photographs were obtained using the Apple iPhone 11 pro max camera (12 megapixels).

Biochemical Assay

A 3-mm punch biopsy was obtained from each area of treatment as a baseline measurement and 4 weeks after the last treatment session. Skin biopsy specimens were kept frozen until assayed. Topical

antiseptic and topical antibiotic were prescribed for the patients twice daily for five days after taking the biopsy. Levels of PDGF and CTGF were measured by Polymerase Chain Reaction test (PCR). RNA was extracted from tissue samples using QIAamp®. RNA Blood kit that was provided by Qiagene (Germany), was available in the Biochemistry Department, Faculty of Medicine, Cairo University. The extracted RNA was reverse transcribed by using QuantiTect Reverse Transcription Kit (cat no. 205310), Qiagene, Germany. DNA samples were then subjected to DNA quantitation and purity assessment using the NanoDrop® (ND)-1000 spectrophotometer (NanoDrop Technologies, Inc. Wilmington, USA). Quantitative real time PCR was done used QuantiNova syber green PCR kit Qiagene (cat no. 208052). Biochemical steps in details are mentioned in appendix 1.

Statistical Analysis

The collected data were coded, entered, and analyzed by computer using a data base software program; Statistical Package for Social Sciences (SPSS) version 26. Qualitative data were represented as frequencies and percent. Chi square (X^2) test was used to detect relation between different qualitative variables. For quantitative variables mean ± standard deviation (SD) and median with range (for not normally distributed data) were computed. Independent t-test (t) was used for detection of difference between different quantitative variables, while nonparametric data was evaluated with Mann-Whitney U test. Normally distributed paired data were compared by paired t-test while non-normally distributed data were compared by Wilcoxon Signed Ranks test. Correlations between quantitative variables were done using Pearson and Spearman's rank–order correlation coefficient (r). The correlation r is always a number between (-1 and 1). Positive r values indicate positive association between the variables, and negative r values indicate negative association. The results were considered statistically significant and highly statistically significant when the significant probability (p value) was < 0.05 and <0.001 respectively.

3. Results

Patients Characteristics

Patients' data are shown in table 1.

Table 1: Descriptive data of the patients

	All patients (n= 30)	Area B1 (IL CS only) (n=15)	Area B2 (IL CS + MN) (n=15)	P value
Age (years) Mean ± SD	23.37 ±6.44	24.8 ±7.399	21.9 ± 5.161	0.318
Gender % Male Female	13 (43.3 %) 17 (56.7 %)	8 (53.33 %) 7 (46.667 %)	5 (33.33%) 10 (66.6 %)	0.462
Fitzpatrick Skin type % Type III Type IV	20 (66.6 %) 10 (33.3 %)	6 (40%) 9 (60%)	14 (93.3 %) 1 (6.6 %)	0.005
Anatomical location n (%) Head Trunk Upper limbs Lower limbs Head and Upper limbs Trunk and Upper limbs	5 (16.67 %) 9 (30 %) 11(36.67 %) 3 (10 %) 1 (3.33 %) 1 (3.33 %)	2 (13.3%) 3 (20 %) 7 (46.6 %) 1 (6.6 %) 1 (6.6 %) 1 (6.6 %)	3 (20 %) 6 (40 %) 4 (26.6 %) 2 (13.3 %) 0 0	0.563
Etiology n (%) Burn Trauma	21 (70 %) 9 (30 %)	9 (60%) 6 (40%)	12 (80%) 3 (20%)	0.427
Duration (months) Mean ± SD	8.417 ± 8	5.497±7.48	11.367±7.617	0.03

Clinical Assessment

Clinical assessments using POSAS scoring system showed significant reduction in mean values of PSAS and OSAS after treatment when compared to mean values before treatment within both areas A and B. There was no statistically significant difference when comparing between before and after POSAS results and percentage of reduction of both areas A and B ($p > 0.05$). There was also no statistically significant difference when comparing between before and after PSAS, OSAS results and percentage of reduction in both areas B1 and B2 ($p > 0.05$) as shown in table 2. Some photos of our patients, before and after treatment are shown in figures 1, 2 and 3.

Table 2: Comparison regarding OSAS and PSAS scoring between area A (FMR) and area B (IL CS ± MN)

Median and IQR	Area A (FMR)	Area B (IL CS ± MN)	P value
OSAS before	24 12.25	20.5 11.5	0.109
OSAS after	16 8	16 7.75	0.023
P value of OSAS	< 0.001	< 0.001	
OSAS Change	7 7.5	7.5 6.75	0.795
% of OSAS Change	31.7%	29.5%	0.256
PSAS before	29 13.5	25 13.75	0.113
PSAS after	18 7.75	16 6.75	0.122
P value of PSAS	< 0.001	< 0.001	
PSAS Change	10 9.75	9 6.75	0.938
% of PSAS Change	30.9%	31.76%	0.552
*p < 0.05 is significant, **p< 0.01= highly significant			

Biochemical Assessments

Biochemical assessments revealed a significant decrease in after treatment mean values of CTGF and PDGF when compared to before treatment mean values within both treatment areas A and B, but there was a statistically significant difference between the two areas regarding CTGF and PDGF percentage of reduction ($p < 0.05$) with higher percentage of reduction detected in area B, as shown in table 3.

There was a significant decrease in after treatment mean values of CTGF and PDGF when compared to before treatment mean values within both areas B1 and B2. Although area B2 showed a more decrease than area B1 in PDGF and CTGF tissue levels and a higher percentage of reduction, the difference did not reach statistical significance ($p > 0.05$), as shown in table 3.

Table 3: Comparison regarding PDGF and CTGF tissue levels in area A (FMR) and area B (IL CS ± MN)

Median and IQR	Area A (FMR)	Area B (IL CS ± MN)	P value
PDGF before	3.16 3.815	3.165 3.71	0.191
PDGF after	2.3 2.315	1.62 1.9	0.01
P value	< 0.001	< 0.001	
PDGF Change	0.745 1.282	1.965 3.538	0.018
PDGF % of Change	26.15 %	47.865 %	0.013
CTGF before	4.56 4.34	4.56 4.875	0.182
CTGF after	2.49 2.255	1.395 2.672	0.011
P value	< 0.001	< 0.001	
CTGF Change	1.33 2.75	2.89 2.172	0.018
CTGF % of Change	26.345 %	61.635 %	0.002
*p < 0.05 is significant, **p< 0.01= highly significant			

Correlations

There were significant negative correlations between duration and both pre-treatment CTGF tissue levels, which indicates the growth factors tissue levels decrease with time ($p < 0.05$).

There was a significant negative correlation between age and PDGF tissue levels ($p < 0.05$), indicating that younger patients had higher tissue levels of PDGF.

Also, there were significant positive correlations between PSAS, OSAS and CTGF pre-treatment values in both treatment areas A and B, in which the increase in PSAS or OSAS values is mirrored with higher tissue levels of CTGF ($p < 0.05$), as shown in table 4.

Table 4: Correlation between levels of PSAS, OSAS, CTGF and PDGF before treatment within areas A and B

Variable	PSAS		OSAS	
	r	P value	r	P value
CTGF (before) in Area A	0.511	0.004	0.464	0.010
PDGF (before) in Area A	-0.224	0.233	-0.141	0.459
CTGF (before) in Area B	0.478	0.008	0.444	0.014
PDGF (before) in Area B	-0.248	0.128	-0.201	0.286

Side Effects

Most of cases didn't complain of any significant side effects. Only 2 patients suffered from skin erosions and hyperpigmentation in area A and 7 patients suffered from hypopigmentation and one patient complained from atrophy in area B. No other complications were reported.

4. Discussion

The current study aimed at comparing the efficacy of FMR versus ILCS injection with or without microneedling in the treatment of hypertrophic scars on clinical and biochemical levels. The authors' results were comparable both clinically and biochemically. Both FMR (area A) and ILCS injection with or without microneedling (area B) treated areas showed significant improvement in all parameters one month after treatment, in the form of decreased POSAS values, as well as reduced tissue levels of both PDGF and CTGF, with no statistically significant difference regarding clinical improvement. However, Area B showed statistically significant lower PDGF and CTGF levels after treatment and higher percentage of change than Area A.

FMR mechanism of action entails local injury induced by dermal penetration of the microneedles, releasing growth factors that stimulate collagen and elastin fibers production, as well as angiogenesis [10]. FMR advance existing technology by adding heat at controlled depths using extra sharp microneedles, promoting more dermal collagen remodeling. FMR treats segments of the skin and soft tissue, leaving islands of untreated areas to reduce recovery time [11].

Non-insulated needles of VIVACE device were utilized in the current study, as radiofrequency (RF) emission delivered over the whole needle length allows better coagulation and heating of higher volumes of dermal tissue compared to insulated needles [12].

We found significant clinical improvement in FMR

treated areas in the form of decreased PSAS and OSAS one month after treatment, as well as reduced levels of both PDGF and CTGF. Various clinical studies have demonstrated efficacy of RF in treating various skin conditions including striae [13, 14], irregular texture [15], rhytids, hyperpigmentation, skin laxity, and acne scars [16]. However, studies that assess the use of FMR in hypertrophic scars are still scarce. Elawar and Dahan, [17] used electronically controlled non-insulated FMR treatment on nineteen patients to treat atrophic acne scars, improve skin texture, and reduce pore size, for 2 to 6 treatments with one-month interval between treatment sessions. They concluded that the FMR treatment is a highly effective minimally invasive treatment option for acne scars, skin texture improvement, and reduction of wide pores size, with a short downtime and high patients' satisfaction rates.

Naouri and Mazer [18] had a retrospective study on twenty patients with a variety of conditions included photoaging, atrophic, burn and acne scars. They were treated with non-insulated FMR. Patient's satisfaction and efficacy were assessed by both patients and physicians using a 10-point score. Although they concluded that FMR is efficacious in treating scars and photoaging, with the advantages of short downtime and very high patient satisfaction, only one of the patients had a post burn scar and the type of the scar was not specified.

Wang et al. [19] found an overall response rate of 86.3%, when patients with burn scars underwent fractional micro-plasma radiofrequency sessions, with an improvement in POSAS values, particularly in scar color, thickness, and pliability. Unlike our study, the scars were described as non-hypertrophic.

Meshkinpour et al. [20] studied the effect of two sessions of Thermage RF device on hypertrophic scars. Unlike our results, no significant differences between the clinical assessments of pre- and post-treatment scars were found. The additive effect of microneedling, which has been shown to stimulate migration and proliferation of keratinocytes and fibroblasts by inducing the release of several growth factors [10] may explain more favorable results in our study. Also, we performed five sessions in our study versus only 2 sessions in theirs.

Our results reaffirmed the efficacy of ILCS injection in treatment of hypertrophic scars, in the form of decreased PSAS and OSAS values after five sessions, as well as reduced tissue levels of both PDGF and CTGF.

Alexander et al. [21] aimed to evaluate and compare the efficacy of combination of fractional CO2 laser and ILCS injection versus ILCS injection alone in the treatment of keloids and hypertrophic scars. Patients were divided into two groups, each group received four treatment sessions. Combination therapy with fractional laser and ILCS injection showed better results when compared to ILCS injection alone, in the treatment of keloids and HTSs.

The addition of microneedling to ILCS injection was hypothesized to add a mechanical effect to the chemical effect of steroids, but unfortunately there was no statistically significant difference between areas B1 (ILCS injection alone) and B2 (ILCS injection followed by microneedling) regarding clinical scores and tissue levels of PDGF and CTGF showed more reduction in area B1 treated with only ILCS injection. This may be due to the small number of patients in the 2 subgroups (only 15 patients in each subgroup) or the mechanism of action of microneedling in improvement of scars by inducing release of growth factors for rejuvenation in contrast to the anti-inflammatory effect of steroids that results in direct reduction of growth factors levels.

In 2018, Busch et al. [22] tested the effect of microneedling using a roller on persistent erythema of hypertrophic scars. Microneedling influences vascularization by stimulating angiogenesis in the post-needling wound healing process. Also, the synthesis of new collagen enhances the vital thickness of the epidermis. Scars showed a significant reduction of erythema, so they concluded that persistent erythema of hypertrophic scars can be considered as an indication for microneedling. In 2019 [23], they also examined the influence of microneedling on mature hypertrophic scars regarding skin elasticity and tension. Microneedling resulted in a reduction in tension and improvement of pathological values of skin tension and elasticity.

Juhasz and Cohen [24] conducted a systematic review on the use of microneedling and FMR used as monotherapy or in combination with topical, surgical, or systemic modalities, for treatment of scars. They included 58 studies with a total of 1845 patients treated for acne scarring, hypertrophic scars, or keloid scars. They concluded that microneedling and FMR treatment are well-tolerated minimally invasive procedures, which result in clinical improvement of scars, with a high level of patient satisfaction and no serious adverse events.

The current study found that clinical improvement of hypertrophic scars after treatment was mirrored by reduced tissue levels of both PDGF and CTGF. We found that tissue levels showed statistically significant reduction after treatment within both treatment areas A and B.

Although TGF-β is the primary factor that drives fibrosis [25], PDGF also plays a pivotal role [26], as it promotes the expression of TGF-β receptor I/II and leads to a chain reaction of fibrosis [27]. In addition, PDGF receptor signaling pathway is involved in both angiogenesis and fibrosis and can be considered a new therapeutic target [28].

Choi et al., [29] found an increased level of PDGF in HTSs compared with normal scars at both 3 months and 12 months post-surgery, in both the epidermis and the dermis. They also found that the expression of TGF-β1 and PDGF was significantly lower in silicone gel sheet-treated scars than in untreated scars at 4 months post-surgery. These results are similar to our findings of statistically significant decrease of PDGF tissue levels after both treatment methods.

Also, CTGF plays an important role in promoting the fibrotic process of hypertrophic scars. CTGF is a downstream mediator of TGF-β activity that is associated with scar and fibrosis [8]. Colwell et al [8] found that hypertrophic scars fibroblasts have both intrinsic up-regulation of CTGF transcription and an exaggerated capacity for CTGF transcription in response to TGF-β stimulation and suggested that blockage of CTGF activity may reduce pathologic scar formation. Liu et al., [30] detected the expression of CTGF gene by PCR and image analysis technique in 5 normal skins biopsies and 15 hypertrophic scars biopsies. The index of CTGF mRNA in the hypertrophic scars were higher than that of normal skin tissue.

In the current study, minimal side effects were observed. Minimal tolerable pain during the treatment sessions, and transient erythema lasting for 2-3 days were experienced in all patients. Hypopigmentation occurred in 7 patients, and one patient complained from atrophy in areas treated with ILCS injection. Hyperpigmentation and skin erosions occurred in two patients in areas treated with FMR. FMR was associated with less downtime. Patients of different skin phototypes can therefore be treated with RF-based systems or microneedling relatively safely.

The limitations of the current study were the small sample size. The authors recommend conducting larger scale future trials with a longer follow up period, including a comparison between ILCS injection alone and combined ILCS and microneedling in treatment of HTSs on a larger scale. In addition, we recommend measuring PDGF and CTGF immediately after treatment and comparing their levels at different stages of follow-up to detect their change with time Also, assessing collagen and elastic fibers changes at histopathological levels before and after treatment, and correlating with growth factors tissue levels.

In conclusion, FMR, ILCS injection and microneedling are effective and safe modalities in the treatment of hypertrophic scars, with comparable results clinically, but better biochemical results with ILCS injection treated areas. FMR is a safe option for treatment of hypertrophic scars with short downtime and rapid healing, besides being safe in dark skinned patients compared to ILCS.

Declarations

Fundingsources: None.

Conflicts of interest: None declared.

Ethics approval: The Research Ethics Committee of the Faculty of Medicine, Cairo University approved this study.

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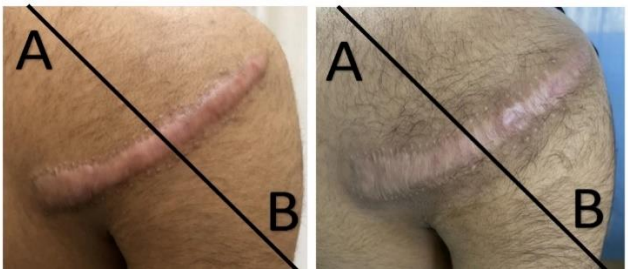

Figure 1: Case 1, a 19-year old male patient with a 20 cm linear hypertrophic scar on the back of the right shoulder. Area A was treated with fractional microneedling radiofrequency, and area B was treated with combined intralesional steroid injection and microneedling.

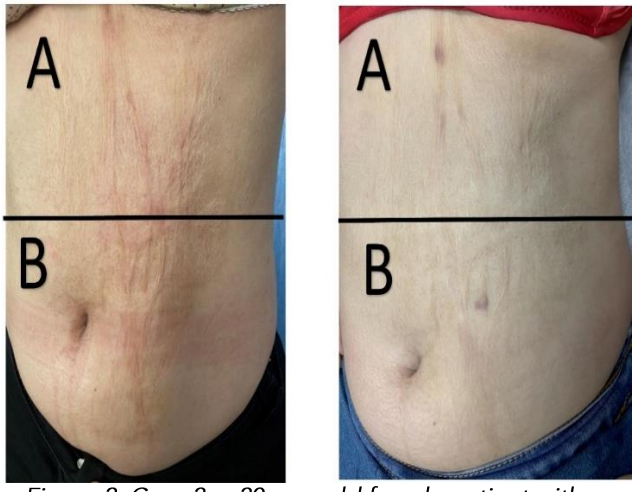

Figure 2: Case 2, a 20-year old female patient with a hypertrophic scar on the back of the left side of the trunk. Area A was treated with fractional microneedling radiofrequency, and area B was treated with combined intralesional steroid injection and microneedling.

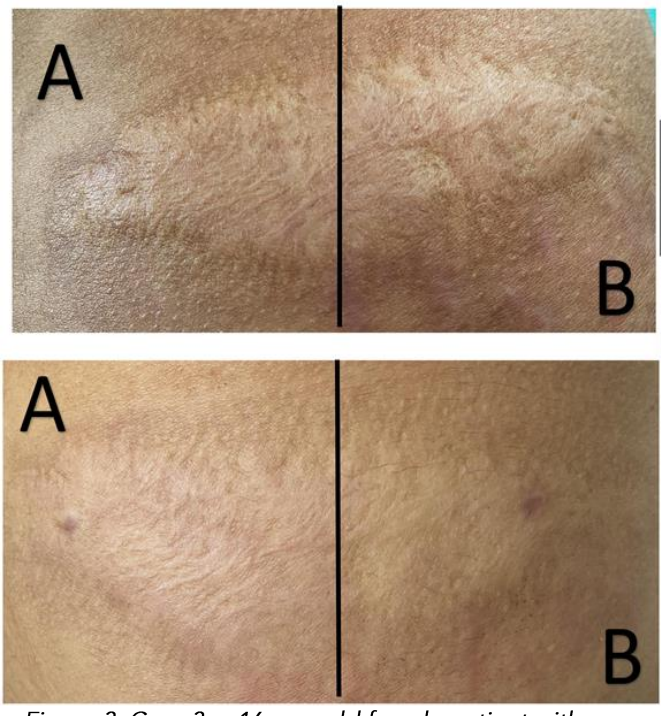

Figure 3: Case 3, a 16-year old female patient with a hypertrophic scar on the back of the right flank. Area A was treated with fractional microneedling radiofrequency, and area B was treated with intralesional steroid i njection.