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Research Article

Comparison of Ultrasound-Assisted Low-Dose Versus Medium-Dose 5-Fluorouracil and Triamcinolone Acetonide in the Treatment of Hypertrophic Scar

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Intralesional 5-fluorouracil (5-FU) and triamcinolone acetonide (TAC) injection is effective for the treatment of hypertrophic scar. The side effects of current that recommended 45 mg/ml (high-dose) 5-FU have been reported. However, no previous study has investigated the efficacy and safety of low-dose (2.5 mg/ml) 5-FU with 4 mg/ml TAC or medium-dose (10 mg/ml) 5-FU with 4 mg/ml TAC for treatment of hypertrophic scar. Herein, a retrospective comparative study was conducted. The records of 70 patients, treated with low-dose (2.5 mg/ml) 5-FU and 4 mg/ml TAC every 4 weeks (Group 1) or medium-dose (10 mg/ml) 5-FU and 4 mg/ml TAC every 4 weeks (Group 2), were analyzed. The Vancouver Scar Scale (VSS), vascularity, and thickness of hypertrophic scar at baseline and at 7th-treatment (each group received 6 treatment sessions) were compared. The ultrasound showed the large vascular distribution in scar margins. Both groups gained clinical improvement in VSS, vascularity, and thickness. Group 2 (medium-dose) exhibited significantly better improvement than Group 1 (low-dose). However, the overall side effects rate was 11.4% in Group 1, significantly lower than 31.4% in Group 2. Scar margins were suggested to be target sites for injection. Medium-dose (10 mg/ml) 5-FU + 4 mg/ml TAC could effectively reduce the thickness of hypertrophic scar; however, the side effects rate was also higher in medium-dose group than in low-dose group.

1. Introduction

Hypertrophic scar is a fibroproliferative skin disease characterized by disordered collagen accumulation. It is still a major clinical problem although various treatments [1] (including the silicon-based products, agents' injection, surgical intervention, radiotherapy, and laser therapy) are suggested. Among these treatments, combination 5-FU with corticosteroid injection is useful for hypertrophic scar treatment. Fitzpatrick [2] first proposes the 50 mg/ml 5-FU for the treatment of hypertrophic scar. Recently, Jiang et al. [3] conducted a meta-analysis of 6 trials from USA, Pakistan, Iran, India, and Thailand. In these trials, the high-dose (45 mg/ml) of 5-FU combined with TAC is recommended and applied; the dosage in 5 trials is 4 mg/ml TAC and 45 mg/ml 5-FU, while in 1 trial is 1 mg/ml TAC and 45 mg/ml 5-FU [4–9]. The topical 5-FU injection with TAC is effective; however, side effects associated with high-dose 5-FU injection, including the extreme pain and ulcerations, are addressed [10]. Laser-assisted topical steroid injection with 10 mg/ml TAC is effective for keloid [11], while there is no comparative study investigating the efficacy and safety of high-dose (45 mg/ml) or medium-dose (10 mg/ml) or low-dose (2.5 mg/ml) 5-FU combined with TAC in treatment of hypertrophic scar.

Different from well recognized standard of 45 mg/ml (high-dose) 5-FU, the drug strength of 5-FU in China is 25 mg/ml [12, 13], and we previously treated patients with medium-dose (10 mg/ml) and low-dose (2.5 mg/ml) 5-FU and TAC. Thus, we retrospectively compared the efficacy

and safety of medium-dose or low-dose 5-FU combined with TAC in treatment of hypertrophic scar.

In the abovementioned 6 trials, the drug is injected until slight blanching is observed and the maximum volume is less than 0.5 ml/cm^2. However, the hypertrophic scar presents various thicknesses in clinic; thus, there is limitation in calculating the amount of drug according to area instead of volume. Until now, there is lack of accurate record for the drug dosage per unit volume and lack of comparative study for the effect of drug at different concentrations. Thus, further investigations are needed.

Herein, we conducted a comparative study to evaluate the efficacy and safety of ultrasound-assisted 10 mg/ml and 2.5 mg/ml 5-FU and TAC for hypertrophic scar.

2. Material and Methods

Following institutional review board approval, detailed patients' characteristics were collected from their medical records. Patients receiving less than 6 treatment sessions were excluded. Thirty-five patients received 2.5 mg/ml 5-FU (Shanghai Xudong Haipu pharmaceutical Co, Ltd., China, 0.25 g/10 ml) and 4 mg/ml TAC (Kunming Jida pharmaceutical Co, Ltd., China, 40 mg/1 ml) every 4 weeks (low--dose group), while 35 patients received 10 mg/ml 5-FU and 4 mg/ml TAC every 4 weeks (medium-dose group) at Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, between Jan 2020 and Aug 2021. The study was conducted according to the Declaration of Helsinki, and informed consent was obtained from the participants.

Each time before injection, all the patients were photographed and received B ultrasound examination performed by surgeon and sonographer in our groups, respectively. The surface areas were estimated with the ruler. Then, the total volume of hypertrophic scar was obtained with the length, width, and thickness. For Group 1 (low-dose), the 4 ml 0.2% lidocaine was used to dilute with 0.5 ml 5-FU and 0.5 ml TAC in a 5 ml syringe. For Group 2 (medium-dose), the 2.5 ml 0.2% lidocaine was used to dilute with 2 ml 5-FU and 0.5 ml TAC in a 5 ml syringe. The mixed solution was transferred into 1 ml syringe and injected with 30-gauge needle, until slight blanching was noticed. The spacing between injected points was approximately 1 cm. The central area of hypertrophic scar was dense with collagen deposition, and the drug was difficult to inject and infiltrate. By analyzing the data of B ultrasound, we mainly injected the drug into the bilateral sides as well as the superficial surface (marginal area). The injected solution dose was recorded to calculate the dose per unit volume.

2.1. Outcome Evaluation. The records of patients at baseline and at 7th-treatment (each group received 6 treatment sessions) were analyzed. The hypertrophic scars were assessed with two blinded plastic surgeons in our groups using the Vancouver Scar Scale. The thickness of hypertrophic scar was assessed with high-resolution ultrasound with 22-MHz probe (Esaote Mylab). The ultrasound assessment and related data analysis were performed by our experienced sonographer, Angang Ding. The thickness of hypertrophic scar was the distance between the ultrasound gel/epidermis border and dermis/subcutaneous fat border. If the shape of hypertrophic scar was irregular, the ultrasound measurements were repeated three times to obtain a mean thickness. The color Doppler was used to detect the vascularity of hypertrophic scar.

2.2. Statistical Analysis. Statistical analyses were performed with SPSS version 11. For comparison of the outcome of pretreatment and post-treatment in each group and between two groups, student's *t*-test and chi-square tests were used. The P value less than 0.05 was considered statistically significant.

3. Results

3.1. Clinical Characteristics of Patients. Of the 70 patients of hypertrophic scar included in this study, 35 received 2.5 mg/ml 5-FU with 4 mg/ml TAC every 4 weeks and 35 received 10 mg/ml 5-FU and 4 mg/ml TAC every 4 weeks. The Fitzpatrick skin types of included patients were III-IV. The clinical characteristics of patients are summarized in Table 1. The main cause of hypertrophic scar is surgery. The mean duration of the lesion was 9.6 ± 5.5 months in Group 1 and $8.7.3 \pm 6.3$ months in Group 2. With ultrasound evaluation, we also observed that most vascular supply for the hypertrophic scar was located near bilateral margins (Supplemental Figure 1).

3.2. Vancouver Scar Scale (VSS) Score. The VSS score decreased significantly following the injection treatment in both groups (Figures 1(a) and 1(d), Figures 2(a) and 2(d), and Table 2). Better changes in VSS score were obtained in Group 2 (mean reduction of 3.9 ± 1.2) than in Group 1 (3.2 ± 1.5, Table 3).

3.3. Thickness. The ultrasound evaluation showed the significant improvement in thickness reduction of hypertrophic scar in both groups (Figures 1(b) and 1(e), Figures 2(b) and 2(e), and Table 2). Mean reduction of thickness of hypertrophic scar was significantly higher in Group 2 (2.7 ± 1.3) than in Group 1 (2.2 ± 0.4, Table 3).

3.4. Vascularity. The ultrasound evaluation showed the significant improvement in vascularity following treatment in both groups (Figures 1(c) and 1(f) and Figures 2(c) and 2(f).

3.5. Side Effects. The overall side effect rates in Group 1 (11.4%) were significantly lower than those in Group 2 (28.6%). Among them, several patients experienced more than one side effect. The main side effects were erythema, ulceration, and hyperpigmentation. No skin telangiectasia was observed or reported in the participants (Table 4).

Table 1: Characteristics of patients.

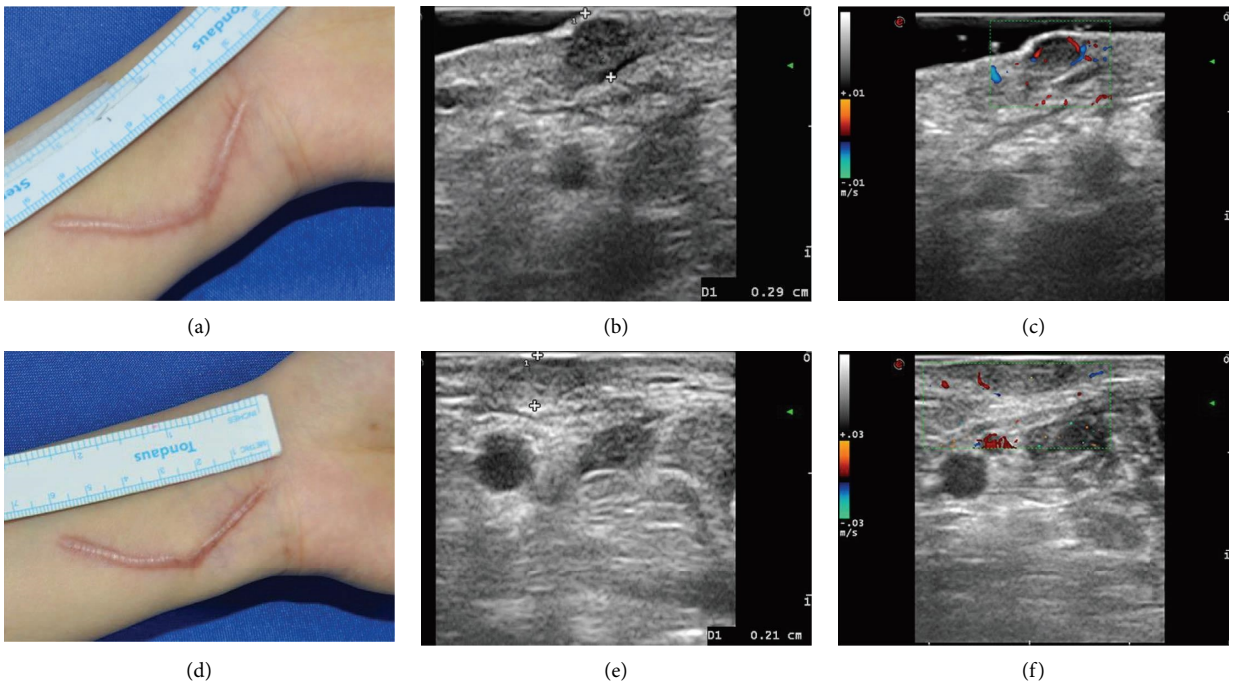
Characteristic	Group 1 ($n = 35$)	Group 2 ($n = 35$)
Mean age (years)	34.2 ± 4.1	36 ± 3.1
Sex, number		
Male	14	12
Female	16	18
Etiology		
Surgery	17	16
Trauma	8	8
Burn	5	6
Location, number		
Neck	1	3
Shoulder	9	11
Forearm	8	7
Abdomen	12	9
Duration (months)	9.6 ± 5.5	8.7 ± 6.3

Table 2: Comparison of outcome in each group (pretopical injection and post topical injection).

		Pre-treatment	Post-treatment	P value
VSS score	Group 1	8.3 ± 1.8	5.1 ± 1.2	<0.05
	Group 2	8.4 ± 1.5	4.5 ± 1.3	
Thickness (mm)	Group 1	4.1 ± 0.3	1.9 ± 0.4	<0.05
	Group 2	4.3 ± 0.4	1.6 ± 0.5	

Table 3: Comparison of effect between two groups.

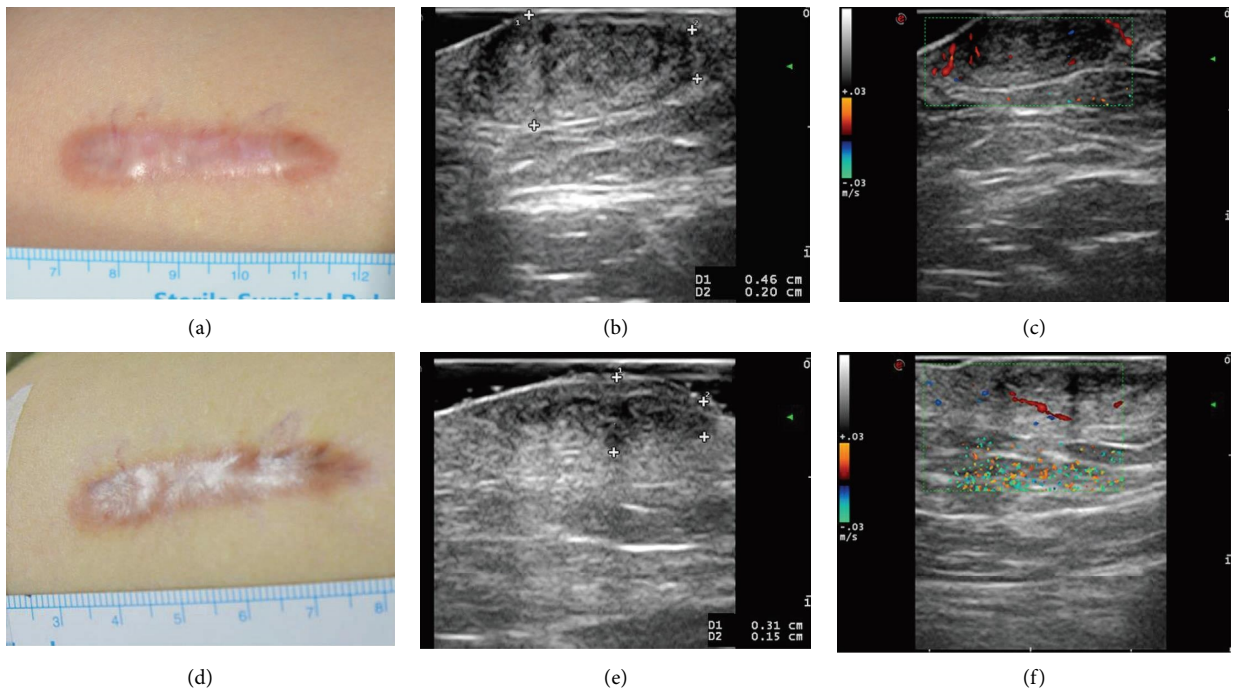
	Group 1	Group 2	P value
Reduced VSS score	3.2 ± 1.5	3.9 ± 1.2	<0.05
Reduced thickness (mm)	2.2 ± 0.4	2.7 ± 1.3	<0.05



(a) (b) (c)

(d) (e) (f)

Figure 1: Representative case in Group 1. A 30-year-old female had postoperation hypertrophic scar in the forearm for 6 months. (a, d) Following the 6 sessions of low-dose 5-FU and TAC treatment, clinical improvement was obtained. (b, e) The ultrasound imaging showed the thickness of hypertrophic scar was reduced. (c, f) The ultrasound imaging showed the vascularity reduction following the injection treatment.



(a) (b) (c)

(d) (e) (f)

Figure 2: Representative case in Group 2. A 34-year-old female had post-operation hypertrophic scar in shoulder for 8 months. (a, d) Following the 6 sessions of medium-dose 5-FU and TAC treatment, the hypertrophic scar was markedly flatter. (b, e) The ultrasound imaging showed the thickness of hypertrophic scar was reduced. (c, f) The ultrasound imaging showed the vascularity reduction following the injection treatment.

Table 4: Comparison of side effects between two groups.

Side effects	Group 1 ($n = 35$)		Group 2 ($n = 35$)		P value
	Frequency	Percentage (%)	Frequency	Percentage (%)	
Overall	4	11.4	10	28.6	<0.05
Erythema	2	5.7	3	8.6	
Ulceration	1	2.9	4	11.4	
Skin atrophy	0	0	1	2.9	
Hyperpigmentation	1	2.9	2	5.7	
Telangiectasia	0	0	0	0	

4. Discussion

Hypertrophic scar represents a dermal fibroproliferative disease characterized by excessive collagen deposition. Although numerous methods, such as silicone, intralesional corticoid injections, botulinum toxin type A, surgical excision, and radiotherapy, have been described for the treatment, these strategies have their drawbacks [14–16]. Among the methods, 5-FU is a common option to inhibit the cell proliferation of fibroblasts through inhibiting thymidine synthase. Several studies demonstrate that the treatment of hypertrophic scar using topical combined TAC and 5-FU injection is effective [4–9]; however, side effects of 45 mg/ml 5-FU (high-dose), including the hyperpigmentation, erythema, and ulceration, are noticed. The side effects of 50 mg/ml 5-FU intralesional injection include the ulceration in 21.4% and burning in 7.1% in 28 patients [17]. Superficial ulceration is also observed in 30% (6/20) patients with 50 mg/ml 5-FU intralesional injection [18].

This is the first study to assess the use of low-dose and medium-dose 5-FU with 4 mg/ml TAC every 4 weeks for hypertrophic scar. Both the low-dose 5-FU with TAC and medium-dose 5-FU with TAC were proven to be efficient while the medium-dose group had better clinical outcomes compared with the low-dose group. Meanwhile, more side effects were observed in medium-dose 5-FU combined with TAC compared with the low-dose 5-FU combined with TAC. The ulceration rates in low-dose group and medium-dose group were 2.9% and 11.4%, respectively, which were lower than high-dose group (21.4% or 30%) as previously reported [17, 18]. As the drug strength of 5-FU in China is 25 mg/ml [13], there were no data about high-dose 5-FU + TAC in the treatment of hypertrophic scar in the current study.

Consider that the formation and progression of hypertrophic scar depended on the cell proliferation of fibroblasts and collagen secretion, which in turn depended on the blood supply. We speculated that injection near the large

blood vessels previously marked by ultrasound could lead to vascular atrophy, which accelerated the inhibition of hypertrophic scar. Thus, it is important to investigate a safe and practical chemotherapeutic therapy with the ultrasound assistance for the hypertrophic scar. Our ultrasound data showed the large blood supply mainly located in the bilateral margin of the hypertrophic scar. With ultrasound, we also observed that the injection targeting the bilateral margins of hypertrophic scar could reduce the vascularity of hypertrophic scar.

In addition, compared with Vancouver Scar Scale (VSS), a subjective tool, mostly used in clinical application, the ultrasound could provide a noninvasive objective assessment including the thickness and vascularity. We demonstrated that ultrasound not only provided an accurate volume information of scar lesion for injection but also was reliable for assessment therapeutic outcome. Compared with optical coherence tomography (OCT), ultrasound has deeper penetration, while OCT has better and finer image resolution than ultrasound [19]; it could be an alternative objective tool for evaluating the outcome for hypertrophic scar treatment, which deserves further investigation.

5. Conclusion

Medium-dose 5-FU combined with TAC is more effective than low-dose group, while the rate of side effects is higher in the medium-dose group. Ultrasound is useful for evaluating the effects of hypertrophic scar intervention.

Data Availability

The data that support the findings of this study are available on request from the corresponding author.

Ethical Approval

The study was approved by the ethical committee of Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine (SH9H-2020-TK234-1), Shanghai, China.

Consent

Written informed consent was obtained from participants.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

RP. Z and YM. L are responsible for the design of study, acquisition of data, analysis, and interpretation of data. AA. D performed the ultrasound evaluation and data analysis. DZ. L participated in the discussion and score. DR. W and RP. Z are responsible for designing the study and revising the manuscript. All authors provided final approval of the manuscript. Yimin Liang and Angang Ding contributed equally to this work.

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Supplementary Materials

Supplemental Figure 1: A 32-year-old female had post-operation hypertrophic scar in the abdomen for 14 months. The volume of hypertrophic scar was calculated using (A) length and width and (B) thickness. (C, D). The ultrasound imaging also indicated the main vascular supply located in the margin of hypertrophic scar. (*Supplementary Materials*)

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