Extracorporeal shockwave therapy for treatment of keloid scars

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ABSTRACT

The purpose of this investigation was to study the effectiveness of extracorporeal shockwave therapy (ESWT) for the treatment of keloid scars, and compared the results with intralesional steroid injection. Thirty-nine patients were randomly divided into 22 in ESWT group and 17 in steroid group. The ESWT group received 3 ESWT treatments in 6 weeks. The steroid group received three intralesional triamcinolone injections in 6 weeks. The evaluations included gross morphology, functional outcome, local blood flow perfusion, biopsy for histopathological examination, and immunohistochemical analysis. Both groups showed significant improvements in appearance with less discoloration, flattening and softer consistency, and more elasticity of the lesions. There is a significant reduction in keloid height after treatment in both groups, and significant differences are noticed between two groups after treatment. The volume of keloid was decreased after treatment but there is no statistically significant difference between two groups. Both groups showed comparable functional scores, POSAS patient, and observer scales. The blood flow perfusion rates were statistically not significant between two groups before and after treatments. Histopathological findings revealed no significant difference in cell count, cell activity, and cell concentration between two groups. After ESWT, the significant decreases in collagen type I, type III, and Masson Trichrome stain were observed as compared with steroid group. However, very little changes were noticed in angiogenesis, inflammatory cytokines, proliferating and regeneration, and apoptosis, with no statistical significance noticed between two groups before and after treatment. This study revealed that ESWT showed comparable functional outcome and POSAS patient and observer scales as compared with steroid injection for keloid scars. Treatment of keloid scars with ESWT resulted in significant decreases in collagen fibers and increases in MMP-13 enzyme.

INTRODUCTION

Keloid is the result of altered wound healing after skin trauma such as surgical incision with excessive scar tissue formation exceeding the confines of the initial wound and does not regress spontaneously. The etiology and pathogenesis of keloids are unknown. Many hypotheses have been proposed as the pathogenesis of keloid formation and growth. Some keloids present with unsightly cosmetic appearance, and others can cause significant discomfort due to pain and pururitus.[1,2] Keloids exhibit exuberant, indefinite growth of collagen over months to form firm broad nodules, often erythematous and with a shiny surface and sometimes with telangiectasias, and tend to occur in darker skinned individuals with a familial tendency and not in the extremes of age.[3–6] The scars frequently recur after surgical excision and show no sign of regression and overgrowth beyond the initial wound area.[7–9]

Keloids differ from hypertrophic scars that usually do not extend beyond the original wound area, often regress spontaneously and rarely recur after excision. While hypertrophic scars usually develop within a few weeks after skin injury, keloids often show a delayed onset, sometimes forming several months after skin trauma. The incidence of keloids was reported ranging from 1% to as high as 16% in different geographic and ethnic distributions.[2] The diagnosis of keloid is a clinical exercise consistent with the firm nodular appearance of keloids, excessive deposition of collagens and other extracellular matrix (ECM) components histologically.[1] Altered transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), fibronectin, hyaluronic acid, and biglycan in extracellular matrix are found in keloids.[10,11] The keloid fibroblasts

have four- to five-fold increases of TGF-β and PDGF. The extracellular matrix of keloid tissues contains elevated fibronectin and proteoglycans and decreased hyaluronic acid.[1] Other hypotheses included collagen turnover hypothesis,[11] tension hypothesis,[12] genetic immune dysfunction,[13] altered keratinocyte-fibroblast interactions,[14] sebum reaction hypothesis,[15] and hypoxic microenvironment.[1,2,16] No single hypothesis adequately explains the mechanism of keloid formation.

Many methods of treatment were proposed for keloid scars. Intralesional steroid injection with triamcinolone (kenalog) is the most effective and widely used treatment for keloids. Triamcinolone inhibits the proliferation of normal and keloid fibroblasts and collagen synthesis, increases collagenase production, and reduces the levels of collagenase inhibitors.[17] Surgical excision alone generally results in recurrence of the keloid lesions because it stimulates additional collagen synthesis resulting in rapid regrowth and often a larger keloid.[18,19] Radiation therapy at the dose of 10–15 Gy as an adjunct therapy immediately after surgical excision shows the efficacy rate of 65–99% in long-term follow-up.[20,21] Radiation therapy increases the rate of apoptosis in keloid fibroblasts, reestablishing cell population equilibrium.[22] Other adjunctive treatments include silicone gel,[23,24] pressure therapy,[25] laser therapy,[26–28] cryotherapy,[29,30] 5-fluorouracil,[31] interferon,[32] retinoids,[33] and the combined therapies.[34,35] The optimal treatments consist of various combinations of triamcinolone, surgical excision, pressure therapy, silicone gel, and occasionally radiotherapy. Most treatment modalities achieved limited success, but none showed universal result. At present, the target therapy remains elusive, and no ideal therapy exists for keloids.

Recently, extracorporeal shockwave therapy (ESWT) was shown effective in acute and chronic wounds,[36] burn lesions,[37] and diabetic foot ulcers.[38] The exact mechanism of ESWT remains unknown. However, ESWT treated lesions showed increased cell proliferation, cell activity, cell concentration, and decreased cell apoptosis, and improvement in blood flow perfusion and tissue regeneration.[38] The hypoxic theory demonstrated that micro-vessels in keloid scars are partially occluded by the proliferation of endothelial cells that result in hypoxic microenvironment.[1] We hypothesize that ESWT may be effective in the treatment of keloid scars. The purpose of this study was to investigate the effectiveness of ESWT in the treatment of keloid scars and compared with intralesional steroid injection with triamcinolone.

METHODS

Study design

The Institutional Review Board in human study approved this study. The declaration of Helsinki protocol was followed and all patients were required to give their written informed consent prior to the participation in the study. The inclusion criteria included patients with keloid scars larger than 1.0 cm by clinical examination. Exclusion criteria included patients with cardiac arrhythmia or pacemaker, pregnancy, skeletal immaturity, patients with malignancy, and poor compliant patients with lacking of complete follow-up data. In this prospective open label randomized case study, 39 patients were randomly divided into two groups with 22 in ESWT group and 17 in steroid group by the closed envelopes containing computer-generated numbers. The flow chat is shown in Figure 1. The patient demographic characteristics are summarized in Table 1. Patients in shockwave group received ESWT, while patients in steroid group received intralesional triamcinolone injection. The evaluations included clinical assessment of the keloids appearance with photo-documentation, functional outcomes for pain score, itching, erythematous change, POSAS patient scale, and POSAS observer scale,[39] focal blood flow perfusion and biopsy for histopathological examination and immunohistochemical analysis.

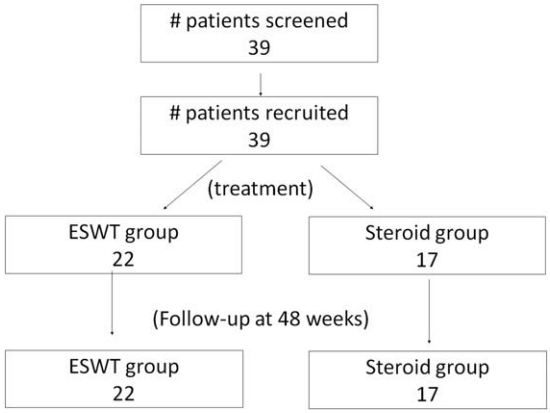

Figure 1. The graphic illustration shows the flow chart of patient recruitment.

Pretreatment evaluations included a complete history and physical examination, assessment of the size, shape, and height of the keloid lesions. The severity of symptoms such as pain, pruritus, and erythematous changes, if any, were graded from 0 to 3 with 0 for no symptoms, and 3 for severe symptoms. The local blood flow perfusion was

Table 1. Patient demographics characteristics

	ESWT group	Steroid group	*p*-Value
No. of patients	22	17	
Average age (years)	35.96 ± 14.55	30 ± 10.3	0.422
(Range)	(18–58)	(18–50)	
Duration (months)	36.45 ± 57.23	20.65 ± 20.62	0.795
(Range)	(3–240)	(3–61)	
Extremity (Right/Left)	13/9	8/9	
Cause of injury:			
Surgery	11	10	
Trauma	11	6	
Infection	0	1	
Idiopathic	0	0	

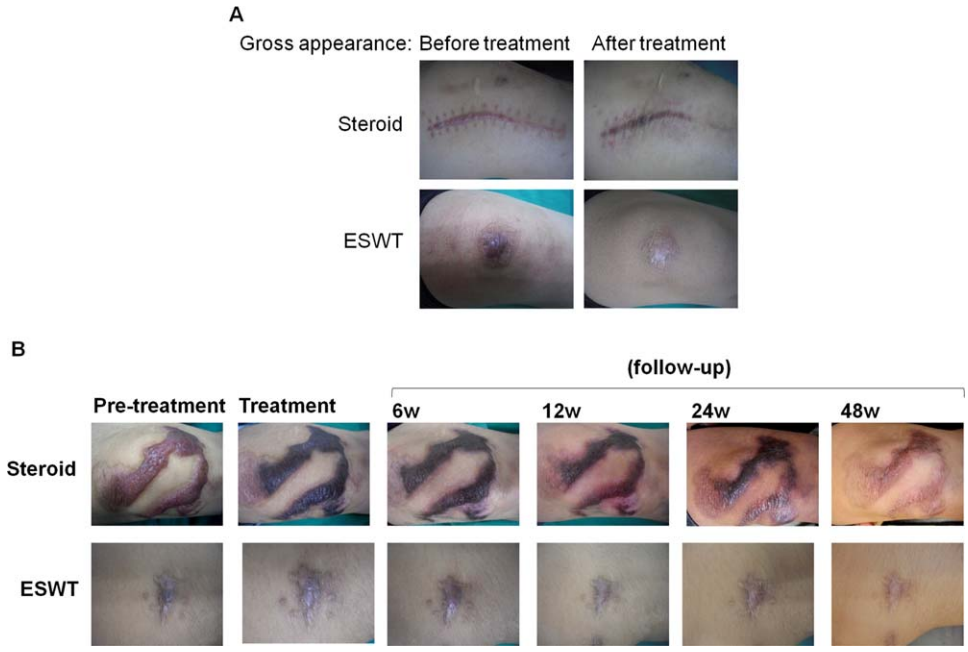

Figure 2. The photographs of gross appearance of keloid scars before and after treatment in steroid and ESWT groups (A), and at different follow-up intervals at 6, 12, 24, and 48 weeks after treatment (B). Both groups showed significant improvements of the keloid scars with less discoloration, flattening, and softer appearance after treatment.

measured using the Peri-Scan PIM II Laser Doppler Perfusion Imager (Perimed AB, Stockholm, Sweden). Local blood flow perfusion scan was repeated at each follow-up. A biopsy was performed at the most prominent lesion site including normal skin edge using a skin biopsy punch (Miltex Inc., York, PA) before and after treatment. The biopsy specimens were subjected to histopathological examination with hematoxylin–eosin (H–E) stain and immunohistochemical analysis including Masson Trichrome stain.

Shockwave application

The source of shockwave was from a dermaPACE device (SANUWAVE, Suwanee, GA). The treatment was performed as an outpatient procedure with no anesthesia. Ultrasound gel was applied to the area of skin in contact with the shockwave applicator. The treatment dosage was lesion size dependent with the numbers of impulses equal to the treatment area in $cm^2 \times 8$, with a minimum of 500 impulses at energy setting E2 (equivalent to 0.11 mJ/mm^2 energy flux density) at a rate of 4 shocks per second. The treatment area was calculated by extending the actual perimeter of the lesion for 1.0 cm in all directions. In shockwave group, each patient received three ESWT treatments in 6 weeks. Post treatment cares included local ice pack and analgesic as needed.

Intralesional steroid injection with triamcinolone

Triamcinolone acetonide (Kenalog 10 mg/mL, Bristol-Myers Squibb, Princeton, NJ) was used in the study. Triamcinolone 10 mg was injected intralesionally per linear centimeter of keloids once every 2 weeks for a total of three injections in 6 weeks. Local care after injection includes ice pack and observation and analgesic if needed.

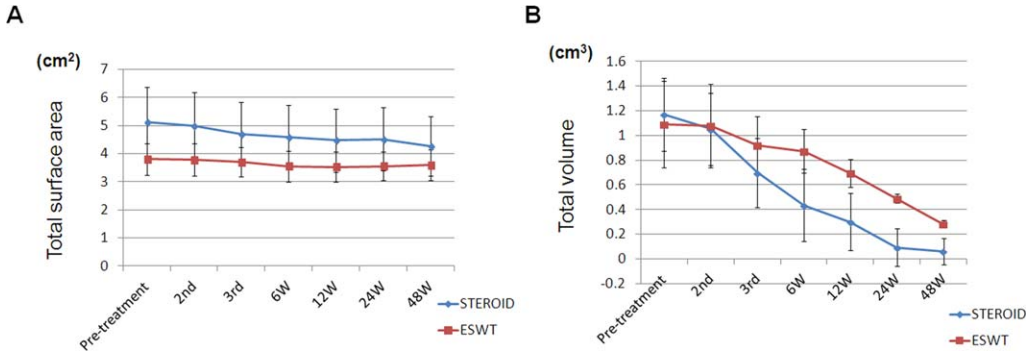

Figure 3. Total surface area (A) and total volume (B) of the keloid lesions showed improvement after treatment with ESWT and steroid. However, there was no difference between the two groups.

Table 2. Functional outcomes

	ESWT group ($N = 22$)			Steroid group ($N = 17$)			p-Value*
Pain score							
Before treatment	2.1 ± 1.3			1.4 ± 1.5			0.105
(Range)	(0–5)			(0–4)			
After treatment	0.2 ± 0.5			0.4 ± 0.9			0.429
(Range)	(0–1)			(0–1)			
p-Value†	0.035			0.022			
POSAS Patient scale‡							
Before treatment	41.2 ± 5.2			36.9 ± 6.7			0.06
(Range)	(31–54)			(26–52)			
After treatment	21.9 ± 10.4			20.0 ± 5.4			0.55
(Range)	(7–24)			(10–23)			
p-Value†	<0.01			<0.01			
POSAS Observer scale§							
Before treatment	36.6 ± 4.5			33.2 ± 7.3			0.06
(Range)	(31–46)			(23–49)			
After treatment	21.3 ± 11.8			18.0 ± 5.6			0.25
(Range)	(7–36)			(10–21)			
p-Value†	<0.01			<0.01			
Itching¶	G1	G2	G3	G1	G2	G3	
Before treatment	11	5	6	5	8	4	0.123
After treatment	18	3	1	16	1	0	0.257

POSAS, The Patient and Observer Scar Assessment Scale V2.0/EN.
*Comparison of the data between ESWT and Steroid groups.
†Comparison of the data before and after treatment within the same group.
‡POSAS patient scales include pain, itching, discoloration, stiffness, thickness, shape, and appearance of the keloid scar.
§POSAS observer scales include vascularity, pigmentation, thickness, relief of pain, pliability, and surface area appearance.
¶Itching: G1, mild; G2, moderate; G3, severe.

Blood flow perfusion scan

The local blood flow perfusion was measured using the Peri-Scan PIM II Laser Doppler Perfusion Imager (Perimed AB, Stockholm, Sweden). The object was placed on a light absorbing background material such as a black or a dark green cloth. The distance between the scanner head and the object was 15 cm. The Min and Max values were set at 0 and 5 V, respectively. The perfusion scan image color scale displays the lowest value in dark blue and the highest value in dark red. LDPI win software in Window 95/98/2000 is used for data analysis including the minimal value, the maximal value and the mean, and standard deviation.

Histopathological examination

The biopsy specimens were fixed in 4% PBS-buffered formaldehyde at 4 °C and embedded in paraffin wax. The specimens were then dissected into 5-μm thick sections with a microtome and subjected to hematoxylin–eosin stain. The cell morphology, cell proliferation, cell concentration, cell activity, and cell apoptosis were examined. The size, thickness, and orientation of the collagen fibers were analyzed microscopically. A pathologist blinded to the study design performed the examination.

Immunohistochemical analysis

The biopsy specimens were further analyzed with immunohistochemical stains for collagen contents including collagen types I, II, III, X, and Masson Trichrome stain, vascular endothelial growth factor (VEGF and CD31), anti-inflammatory cytokines (TGFβ1 and IL6), proliferating and regeneration biomarkers (PCNA and fibronectin), degrading enzyme (MMP-13), and apoptosis bio-markers (TUNEL and caspase-3). The specimens are fixed in 4% PBS-buffered formaldehyde and embedded in paraffin wax, and then cut longitudinally into 5-μm thick sections and transfer to poly-lysine-coated slides. Sections of the specimens are immunostained with specific reagents to identify collagen fibers, angiogenesis, anti-inflammatory cytokines, proliferative, and apoptosis (Santa Cruz Biotechnology Inc., Dallas, TX). The immuno-reactivity in specimens was demonstrated using a horseradish peroxidase (HRP)-3′,3′-diaminobenzidine (DAB) cell and tissue

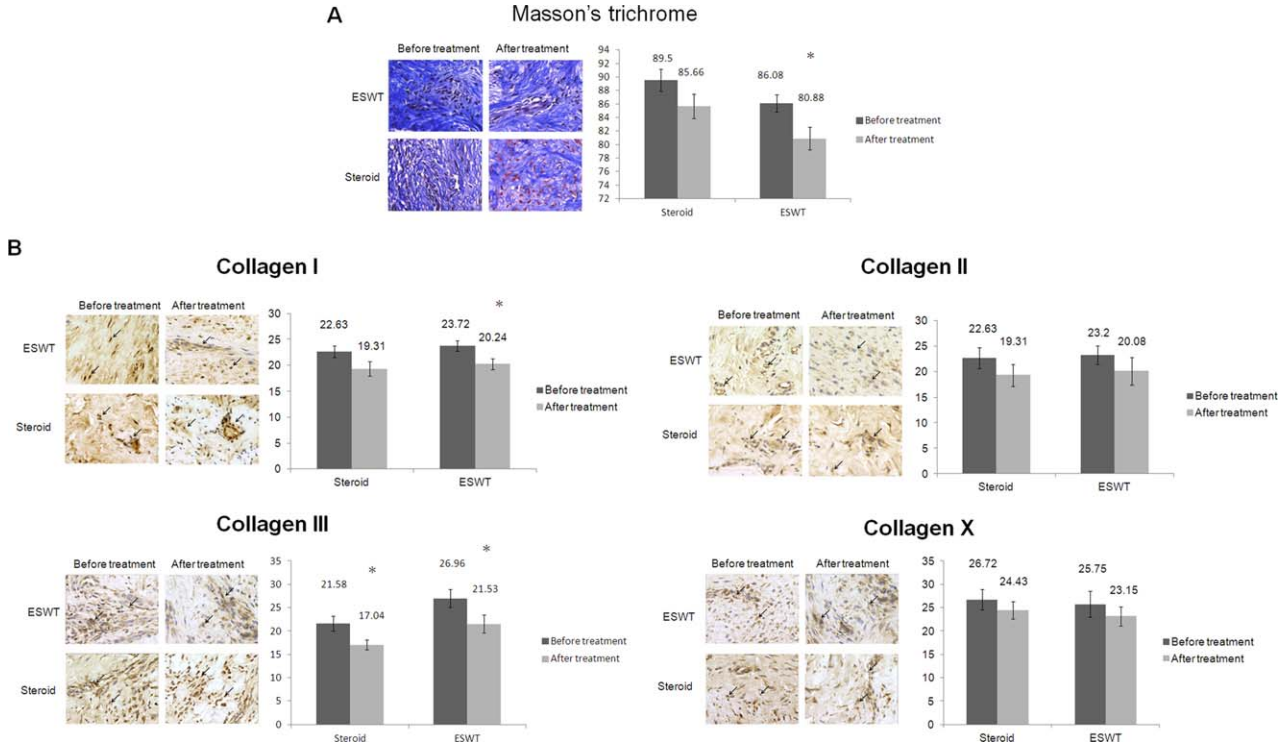

Figure 4. The Masson Trichrome stain (A) and collagen fibers (B) for total collagen content after treatment with steroid and ESWT. ESWT group showed significant decreases of collagen content as compared with the steroid group.* $p < 0.05$.

staining kit (R&D Systems, Inc, Minneapolis, MN). Immuno-activities were quantified from five areas in three sections of the same specimen using a Zeiss Axioskop 2 plus microscope (Carl Zeiss, Gottingen, Germany). All images of each specimen were captured using a Cool CCD camera (SNAP-Pro c.f. Digital kit; Media Cybernetics, Silver Spring, MD). Images were analyzed using an Image-Pro Plus image-analysis software (Media Cybernetics, Silver Spring, MD). The percentage of immuno-labeled positive cells over the total cells in each area was counted.

Statistical analysis

A power analysis reveals that a sample size of 17 in each group would be required to establish the statistical significance with $\alpha = 0.05$ and power = 0.8 assuming a 45% therapeutic difference between the two groups. Overall, 39 patients with 22 patients in the ESWT group and 17 patients in the steroid group were enrolled in the study. The data before and after treatment within the same group were compared statistically using paired *t*-test. The differences between the ESWT group and the steroid group were compared statistically using Mann–Whitney "*U*" test. The statistical significance was set at $p < 0.05$.

Follow-up examinations

Patients were followed up in 6, 12, 24, and 48 weeks after completion of the last treatment. Clinical assessments of the keloid lesions including the length, width, and height are measured, and the appearance of the lesions was photo documented on each visit examination. The severity of symptoms was graded in similar fashion as before treatment. The blood perfusion scan was repeated at each follow-up visit.

RESULTS

The gross appearances of the keloids in planimeter measurements of total surface areas and total volume of the lesions before and after treatment are summarized in Figures 2 and 3 and Supporting Information Table S1. Both groups showed significant improvement in the appearance of keloid scars with less discoloration, softer, and flattening in consistency. There was a significant reduction in keloid height after treatment in both groups, but the volume of keloid was no significant difference between two groups (Figure 3B and Table S1). In histopathology, both groups showed comparable cell activity, cell proliferation, cell concentration, and cell apoptosis. The functional outcomes for pain, itching, erythematous change, and pruritis are shown in Table 2. Both groups showed comparable results with no significant difference in POSAS patient scale and POSAS observer scale between the two groups ($p = 0.06$). The local blood flow perfusion scans showed 0.02 ± 0.01 before treatment and 0.01 ± 0.02 after treatment ($p = 0.125$) for the ESWT group, whereas 0.02 ± 0.02 before treatment and 0.01 ± 0.003 after

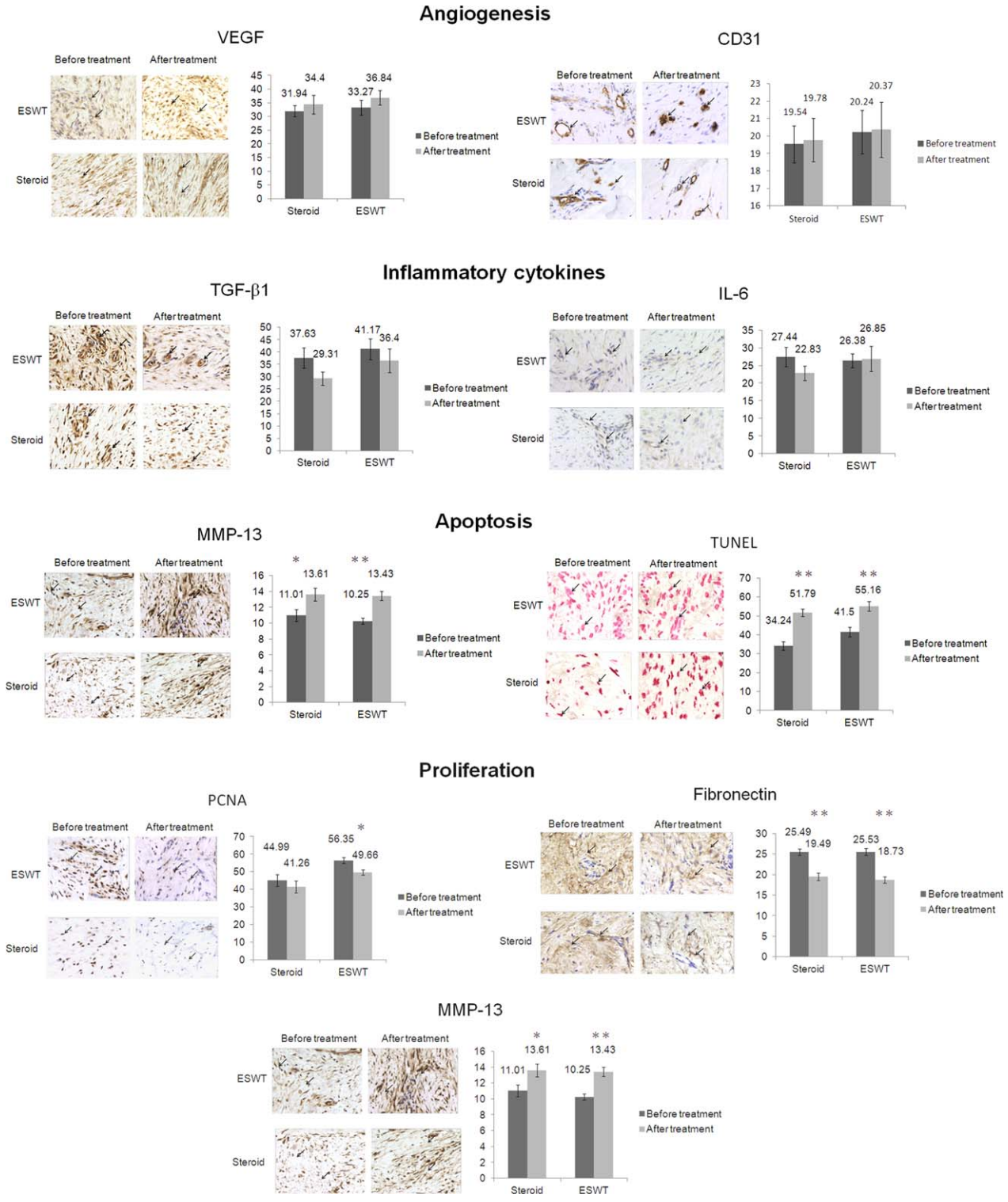

Figure 5. Immunohistochemical analyses revealed very little changes in angiogenesis, anti-inflammatory cytokine, proliferating and regeneration, apoptosis, and MMP-13 after treatments with ESWT and steroid. However, no significant differences were noticed between two groups. $*p < 0.05$ and $**p < 0.001$.

treatment ($p = 0.095$) for steroid group. Both ESWT and steroid groups showed comparable blood flow perfusion with no significant difference between two groups ($p = 0.540$, 0.237) before and after treatment.

The collagen contents in immunohistochemical analysis including Masson Trichrome stain and collagen fibers types I, II, III, X for total collagen content are shown in Figure 4 and Supporting Information Table S2. Other studies included VEGF and CD31 for angiogenesis, TGF-ß1 and IL6 for inflammatory cytokines, PCNA and fibronectin for proliferating and regeneration, degrading enzyme (MMP-13), and caspase-3 and TUNEL for apoptosis, are summarized on Figure 5 and Supporting Information Table 3. Overall, significant decreases in collagen fibers type I, type III, and Masson Trichrome stain and increases in MMP-13 were noted after ESWT as compared with steroid injection. However, very little changes were observed in angiogenesis, proliferative and regeneration, anti-inflammatory, and apoptosis biomarkers with no significant difference noticed between two groups before and after treatment.

DISCUSSIONS

The etiology and mechanism of keloid scars remain unknown. Likewise, there is no best method of treatment for keloid scars. Many treatments were proposed for keloids including steroid injection, surgical excision, radiation therapy, laser therapy, pressure therapy, cryotherapy, silicone gel, 5-flurourasi, interferon, retinoid, and combined therapies. Each modality achieved some successes, but none showed universal results. At present, the target therapy remains elusive, and no ideal therapy exists for keloid scars. Intralesional injection with triamcinolone is considered the most effective method of treatment for keloid scars.

The results of the current study revealed a significant reduction in keloid height after treatment in both groups. ESWT group showed comparable functional outcome in POSAS patient scale and POSAS observer scale as compared with steroid injection in the treatment of keloid scars. The target of Masson Trichrome is the total collagen contents. Collagen contents reduced after treatment and the keloid scars tend to move toward matrix remodeling. The collagen II is a nonprincipal collagen in keloids, therefore, the reduction is obvious than collagen I and III. Collagen III is excessively secreted by fibroblast in early keloids; it is an abnormal ECM deposition. The keloid tends to move toward normal skin recovery by the degradation of collagen II, MMP-13, an enzyme to decompose collagens. The increase of MMP-13 induced collagen degradation, and keloid bundles become flatter.[1,3,14,17]

Triamcinolone inhibits the proliferation of normal and keloid fibroblasts and collagen synthesis, increases collagenase production, and reduces the levels of collagenase inhibitors.[17] ESWT acts as mechanotransduction that induces biological responses including angiogenesis and tissue regeneration. In this study, the pharmacological effects of triamcinolone and mechanical effects of ESWT produced comparable biological behaviors that eventually lead to tissue repair and regeneration.[40] The simple, convenient, and safe noninvasive ESWT may become a treatment of choice in keloid scars.

There are limitations to this study. The small sample size may result in weaker point of statistical analysis. The comparison between the pharmacological agent (triacimnolone) and the mechanical response of ESWT in biological tissue is not a common practice. Perhaps, expansion of the experimental agents such as the specific target of treatment may be worthwhile thinking in future studies. ESWT more likely will become an alternative modality in the treatment of keloid scars.

In conclusion, ESWT showed comparable functional outcome, POSAS patient scale and POSAS observer scale clinically, and significant reduction in collagen fibers and increases of MMP-13 degrading enzyme as compared with intralesional steroid injection.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site