Extracorporeal Shockwave Therapy for Treatment of Keloid Scars

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Disclosure

This study was supported in part and in total from a grant. The source of grant is Chang Gung Research Fund with project numbers CMRPG8B0191, CMRPG8B0192 and CMRPG8B0193.

The presenter received no honoraria or consultancy fee in making this presentation. The presenter services as a member of Advisory Committee of SANUWAVE (Alpharetta, GA). However, this study is irrelevant to the appointment.

Introduction (1)



- Keloid is the result of altered wound healing with excessive scar tissue formation exceeding the confines of the initial wound.
- Keloids differ from hypertrophic scars that usually develop within a few weeks after skin injury, often regress spontaneously and rarely recur after excision.
- Keloids often showed a delayed onset for several months and often extend beyond the confines of the original wound.

Introduction (2)



- The incidence of keloid was reported ranging from 1% to 16% in different geographic and ethnic distributions.
- Many hypotheses were proposed in keloid scars, however, no single hypothesis adequately explains the mechanism of keloid formation and growth.
- The diagnosis of keloid is a clinical exercise consistent with the firm nodular appearance, excessive deposition of collagens and extracellular matrix (ECM) components histologically.

Introduction (3)



- Intralesional steroid injection with triamcinolone (kenalog) is considered the most effective and widely used method of 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.
- Surgical excision alone generally results in recurrence of keloid lesions because it stimulates additional collagen synthesis resulting in rapid re-growth to a larger keloid.

ESWT vs Keloid Scars

- Recently, extracorporeal shockwave therapy (ESWT) was shown effective in acute and chronic wounds, burn lesions, and diabetic foot ulcers.
- ESWT treated lesions showed increased cell proliferation, cell activity, cell concentration, and decreased cell apoptosis. ESWT also improved blood flow perfusion and tissue regeneration.





Purpose of the Study

The purpose of this study was to investigate the effectiveness of ESWT in treatment of keloid scars and compared the results with intralesional steroid injection with triamcinolone.

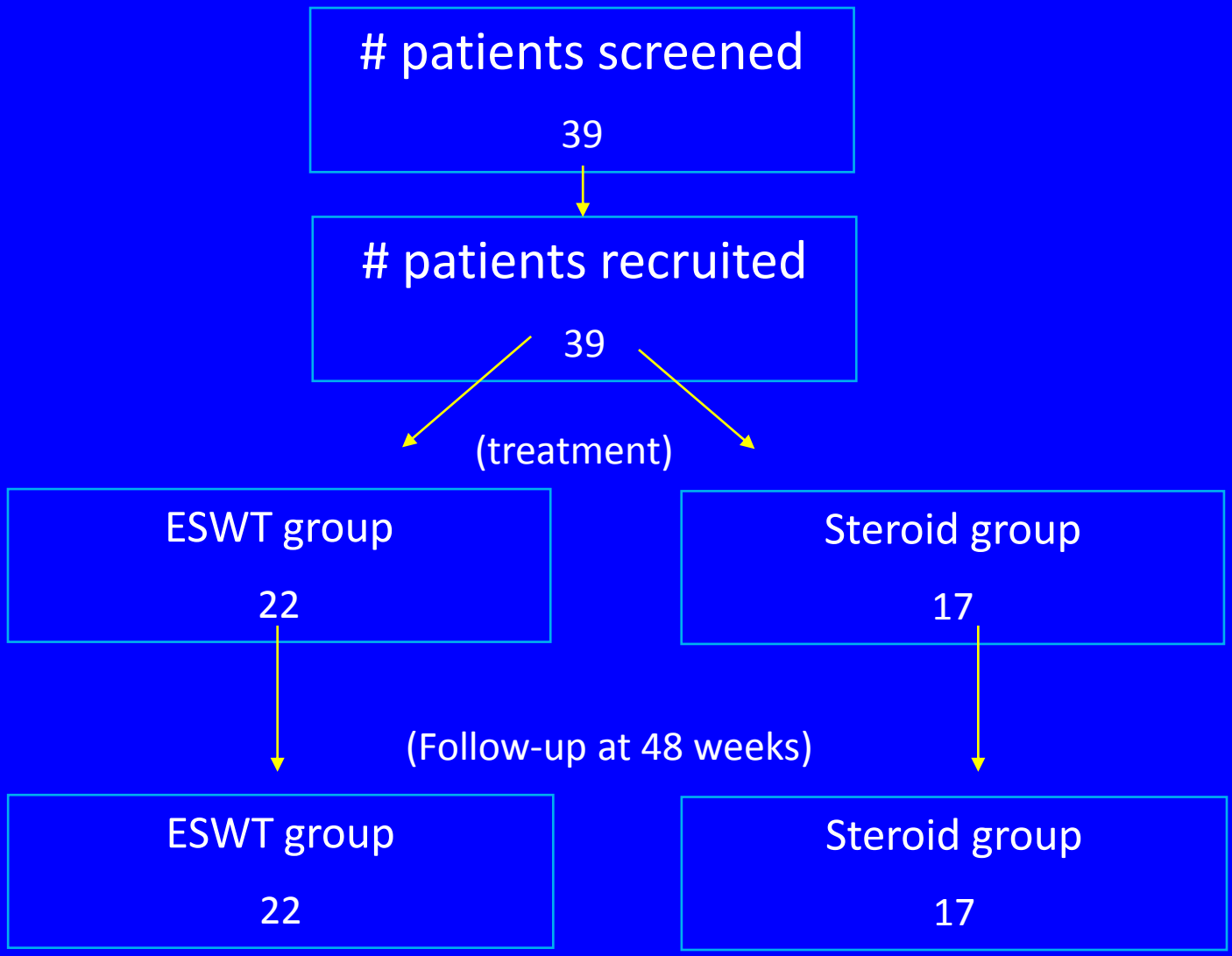




Inclusions and Exclusions

- The inclusion criteria included patients with keloid scars larger than 1.0 cm by clinical examination.
- The exclusion criteria included patients with cardiac arrhythmia or pacemaker, pregnancy,
- skeletal immaturity, patients with malignancy and poor compliant patients.

The flow chart of patient recruitment



ESWT Protocol

The ESWT dosage was lesion size dependent.

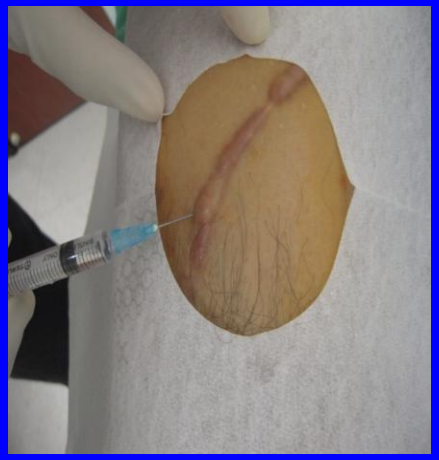
The numbers of impulse equal to the treatment area in cm^2 x 8, with a minimum of 500 pulses at E2 (=0.11mJ/mm^2 EFD) at a rate of 4 shocks per second. The treatment area was calculated by extending the actual perimeter of the lesion for 1.0 cm in all directions..

Each lesion received three courses of ESWT. Each course consisted of one treatment every two weeks for a total of 3 treatments in 6 weeks.



Intralesional Steroid Injection

- Triamcinolone acetonide (Kenalog 10 mg/cc, Bristol-Myers Squibb, Princeton, NJ) was used in this study.
- Triamcinolone 10 mg was injected intralesionally per linear centimeter of keloid once every two weeks for a total of three injections in 6 weeks.



The Evaluation Parameters

(1). Gross appearance of keloid lesions.

(2). Functional outcomes including POSAS patient scale and POSAS observer scale.

(3). Local blood flow perfusion scan.

(4). Biopsy for histomorphological examination and immunohistochemical analysis.

POSAS scales
(The Patient and Observer Scar Assessment Scale)

- The POSAS patient scales included pain, itching, discoloration, stiffness, thickness, shape and appearance of keloid scars.
- The POSAS observer scales included vascularity, pigmentation, thickness, relief of pain, pliability and surface area appearance.

Gross Appearance

Before treatment

After treatment

ESWT group



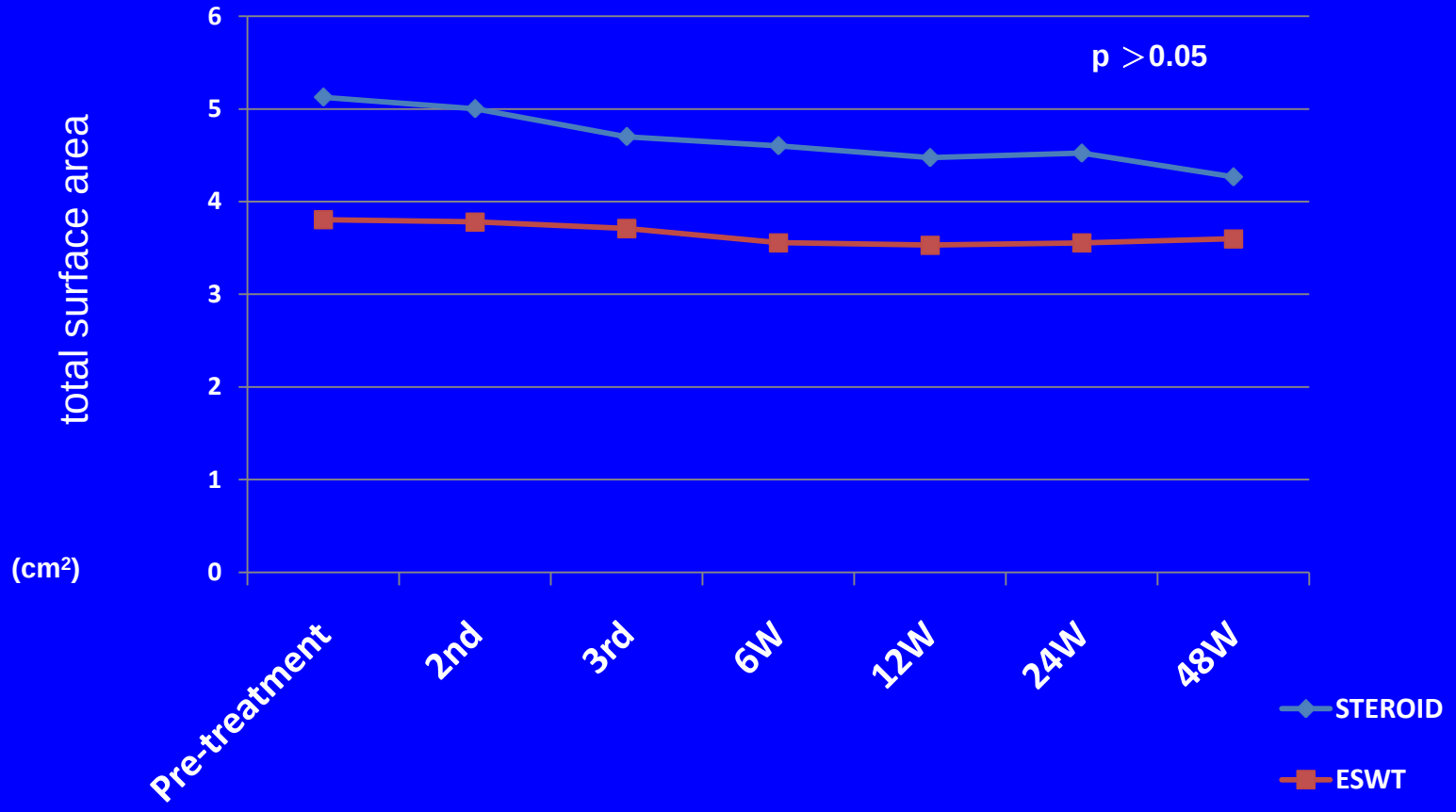


Steroid group





keloid size measurements
(Total surface area)



keloid size measurements
(Total volume)



Gross Appearance of the Lesions
(in brief)

The gross appearance of the keloid scars showed significant improvement after treatment in 88% of steroid group and 95% of ESWT group. The recurrence rates were 5.9% for steroid group and 0% for ESWT group respectively. The keloid scars showed less discoloration, softer and flattening consistency and more elasticity after treatment. However, no significant differences were noticed between two groups before and after treatment ($P > 0.05$).

Complications

- Three cases in steroid group developed infection at the biopsy site. All wounds were successfully treated with wound care and oral antibiotics. No infection occurred in ESWT group.
- There was no device related problems. There was no neurovascular or systemic complications.

Case Illustration (ESWT)



At one year after three courses of ESWT treatment.

Case Illustration (Steroid injection)

pre



2nd



3rd



6 weeks



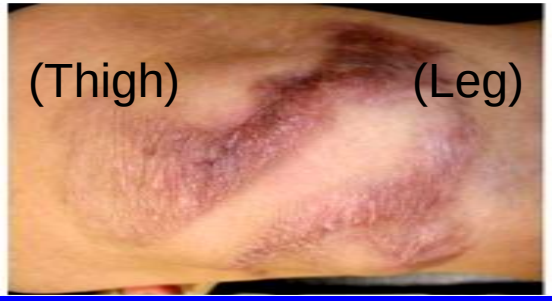
3 months



6 months



1 year



At one year after three kenalog injections..

Functional Outcomes

	ESWT group (N =22)	Steroid group (N =17)	P-value[1]
Pain score			
Before treatment (Range)	2.1±1.3 (0~5)	1.4±1.5 (0~4)	0.105
After treatment (Range)	0.2± 0.5 (0~1)	0.4±0.9 (0~1)	0.429
P-value[2]	0.035	0.022	
POSAS Patient scale*			
Before treatment (Range)	41.2±5.2 (31~54)	36.9±6.7 (26~52)	0.06
After treatment (Range)	21.9±10.4 (7~24)	20.0±5.4 (10~23)	0.55
P-value[2]	< 0.01	< 0.01	
POSAS Observer scale**			
Before treatment (Range)	36.6±4.5 (31~46)	33.2±7.3 (23~49)	0.06
After treatment (Range)	21.3±11.8 (7~36)	18.0±5.6 (10~21)	0.25
P-value[2]	< 0.01	< 0.01	
Itching#	G1 G2 G3	G1 G2 G3	
Before treatment	6 5 11	4 8 5	0.123
After treatment	1 3 18	0 1 16	0.257

POSAS: The patient and Observer Scar Assessment Scale V2.0 / EN.

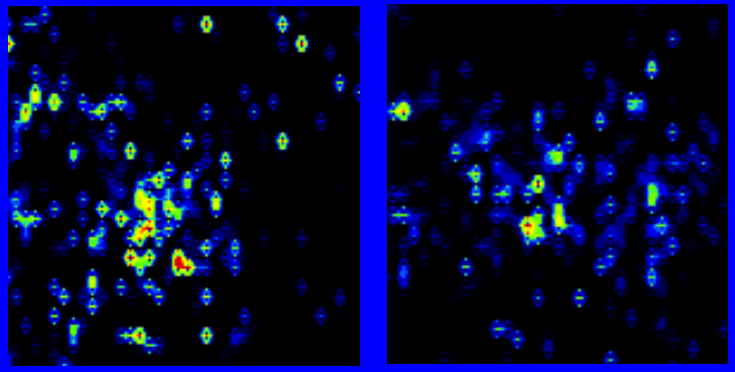
Functional Outcomes in brief

- Both groups showed significant improvements in POSAS patient scales and POSAS observer scales in functional outcomes before and after treatment.
- However, the data were comparable between two groups with no statistically significant differences in POSAS patient scales and POSAS observer scales of functional outcome.

Blood Flow Perfusion Scan
(LDPI Laser Doppler Perfusion Imaging)

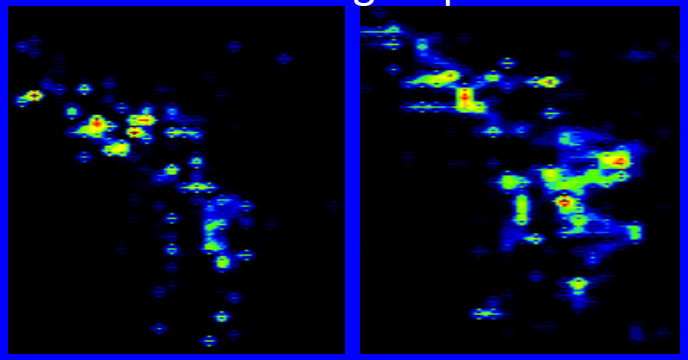
	Before treatment	After treatment	P-value[1]
ESWT group (N=22)	0.02 ± 0.01	0.01 ± 0.02	0.735
Steroid group (N=17)	0.02 ± 0.02	0.01 ± 0.003	0.083
P-value[2]	0. 815	0.435	

ESWT group



Before treatment After treatment

Steroid group



Before treatment **After treatment**

Local Blood Flow Perfusion in brief

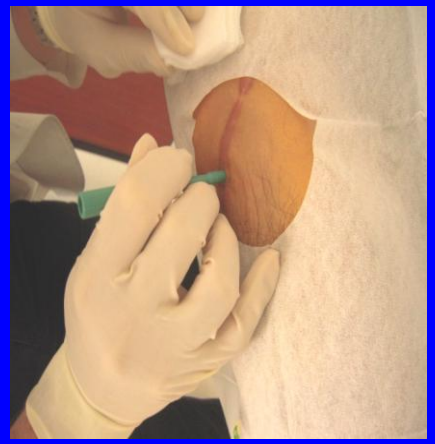
- ESWT group and steroid group showed comparable blood flow perfusion with no significant difference in blood flow perfusion rates noticed between two groups before and after treatment. ($P > 0.05$).

Biopsy of the lesions

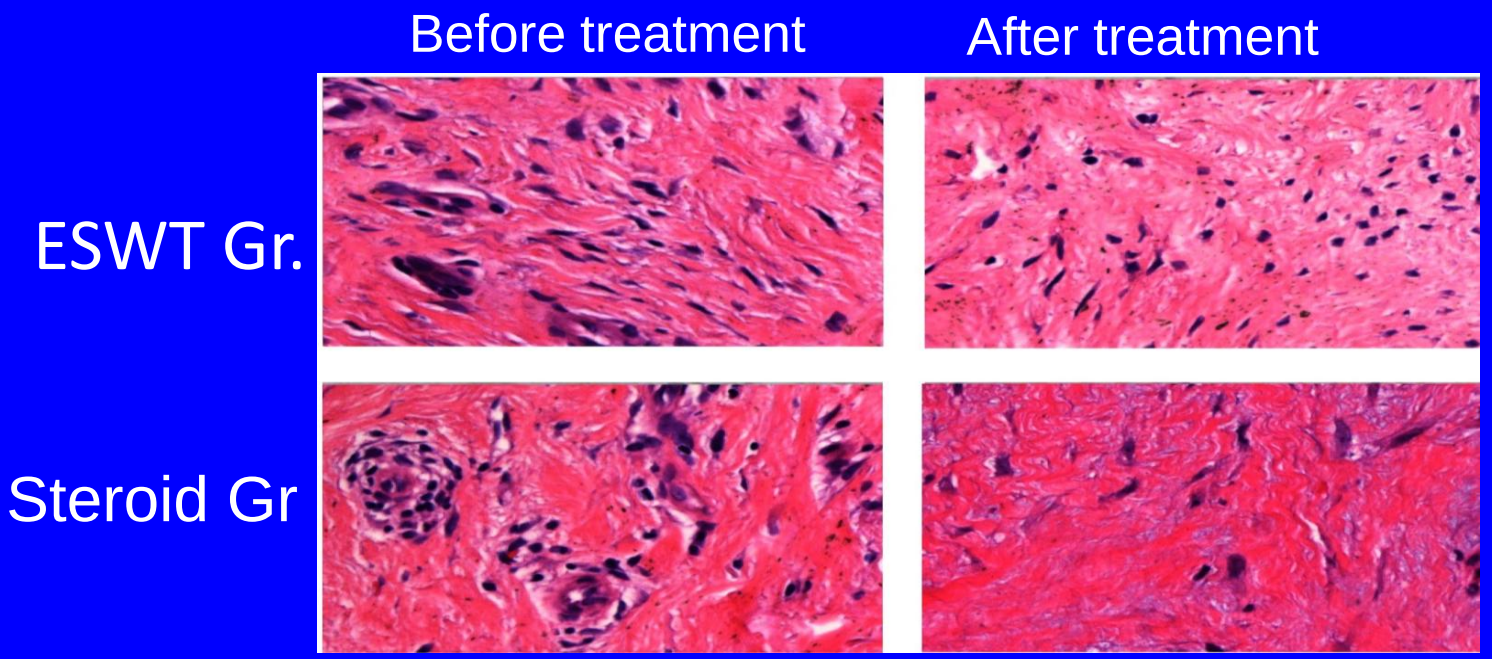
Biopsy of the lesion was performed at the most prominent lesion site including normal skin edge using a skin biopsy punch (Miltex Inc, York, PA) before and after treatment.

The biopsy specimens were subjected to histomorphological examination with H-E stain, and IHC analyses for collagen fibers including Masson Trichrome stain and changes in molecular biomarkers.





Histomorphology



Tissue morphology included the size, thickness and orientation of collagen fibers type I, type II, type III, type X and Masson Trichrome stain for total collagen content.

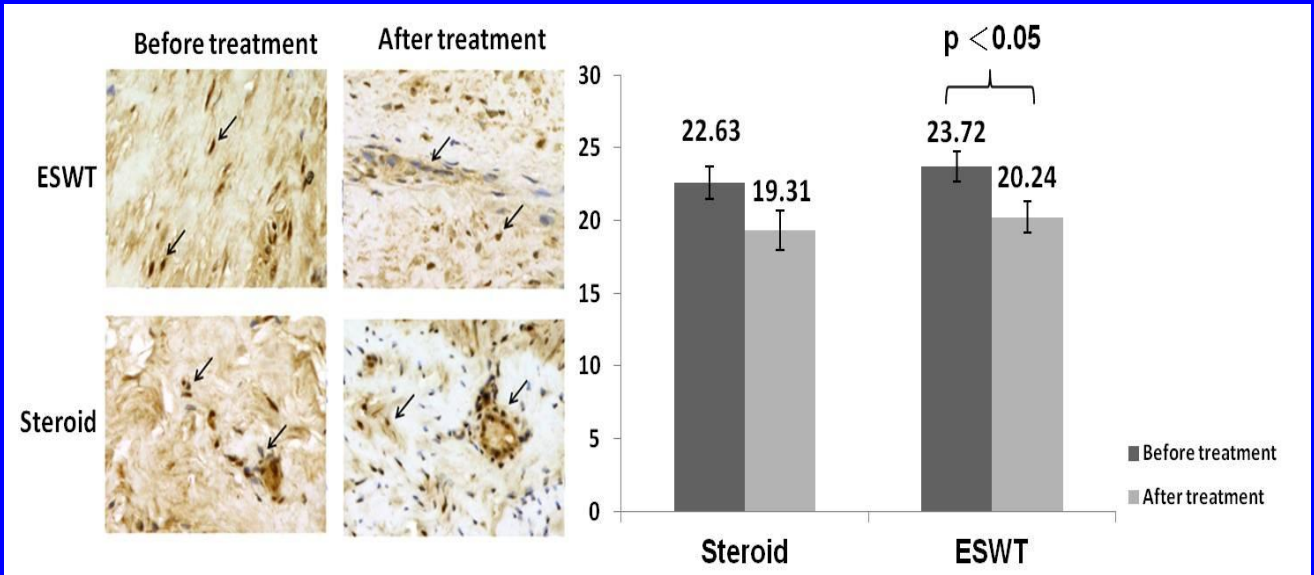
Cell morphology included cell activity, cell concentration, cell proliferation and cell apoptosis.

Histomorphology in brief.

- In tissue morphology, both groups showed similar size, thickness and orientation of collagen fibers. In cell morphology, comparable cell activity, cell proliferation, cell concentration and cell apoptosis were noticed between two groups. The differences in tissue histomorphology between two groups are statistically not significant ($P > 0.05$).

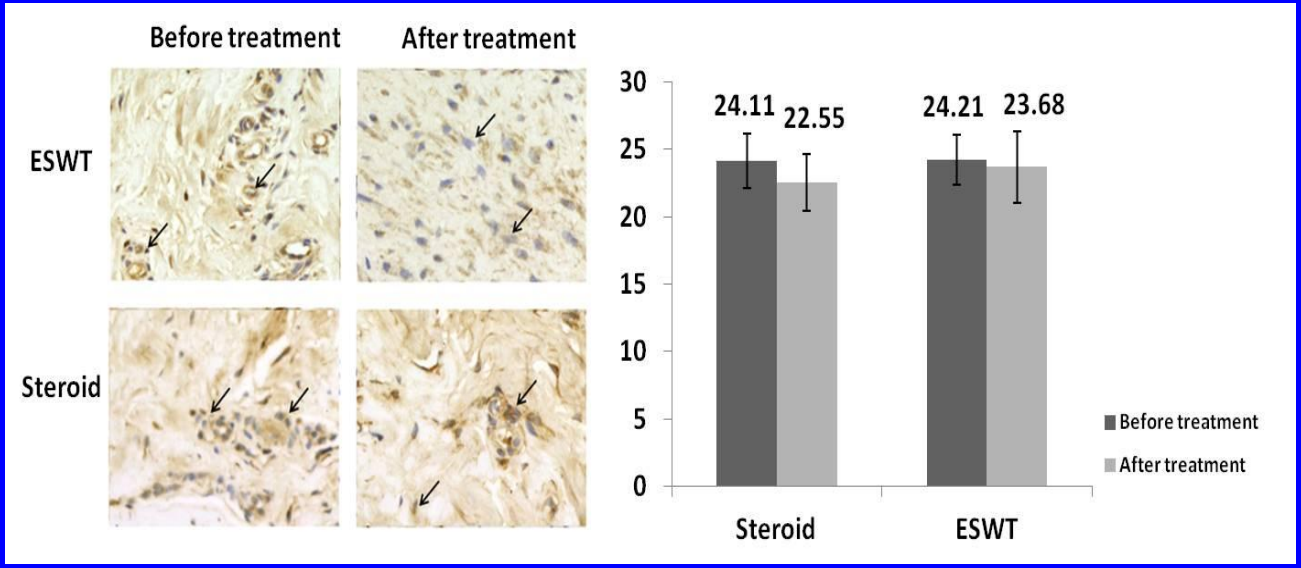
Collagen fibers

Collagen I



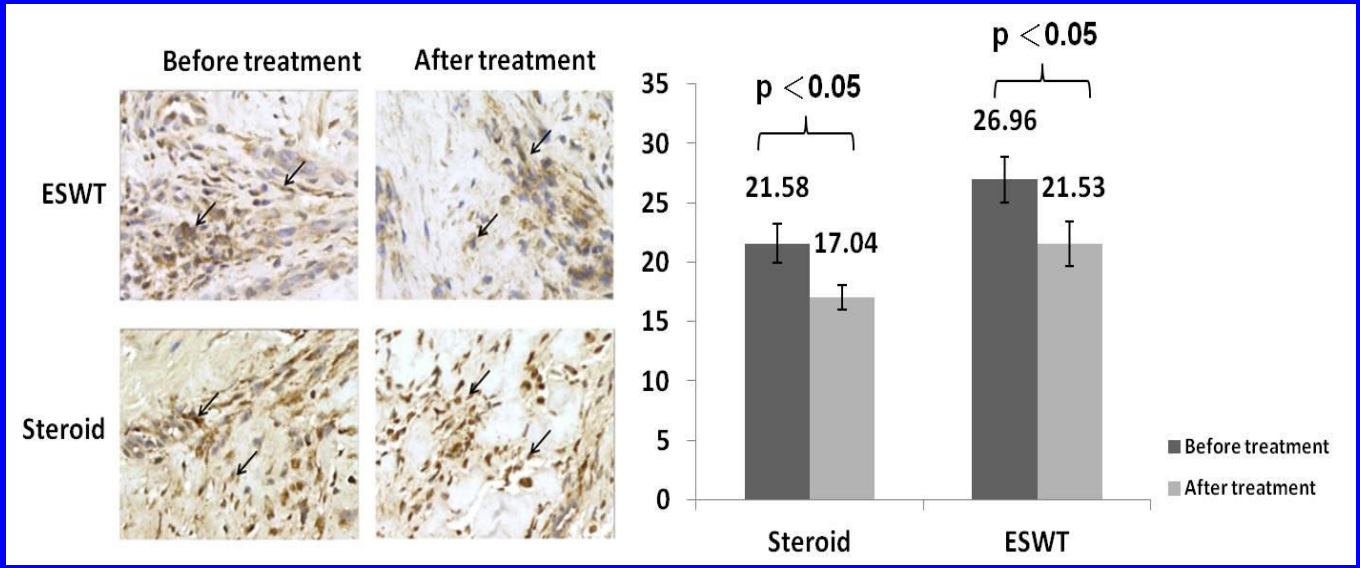
Collagen fibers

Collagen II



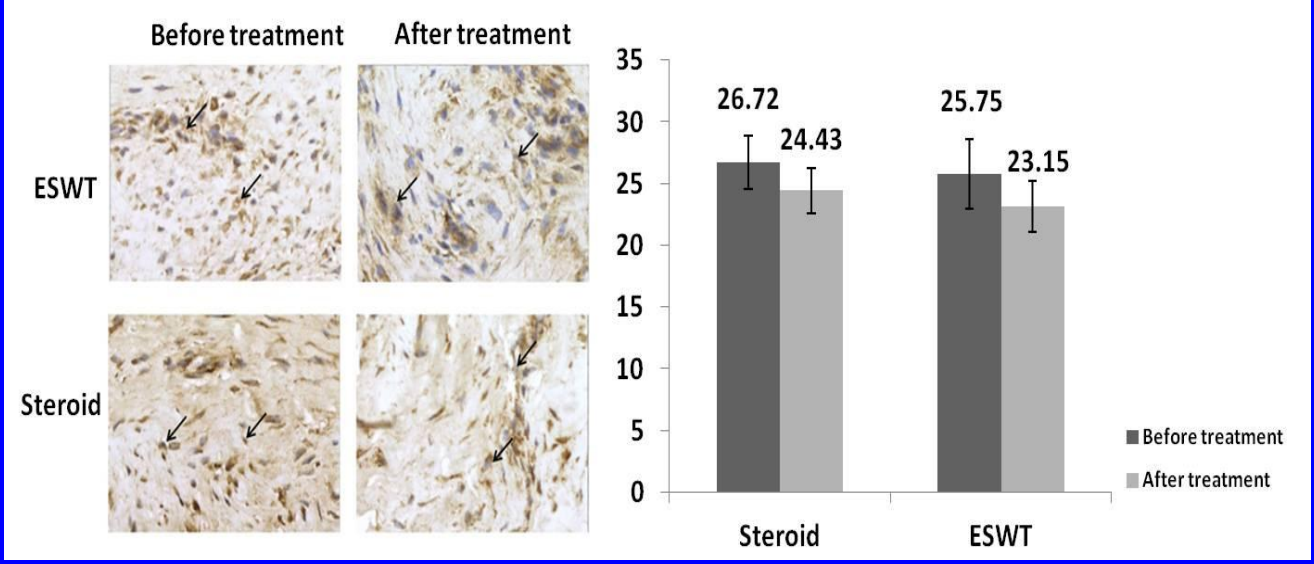
Collagen fibers

Collagen III



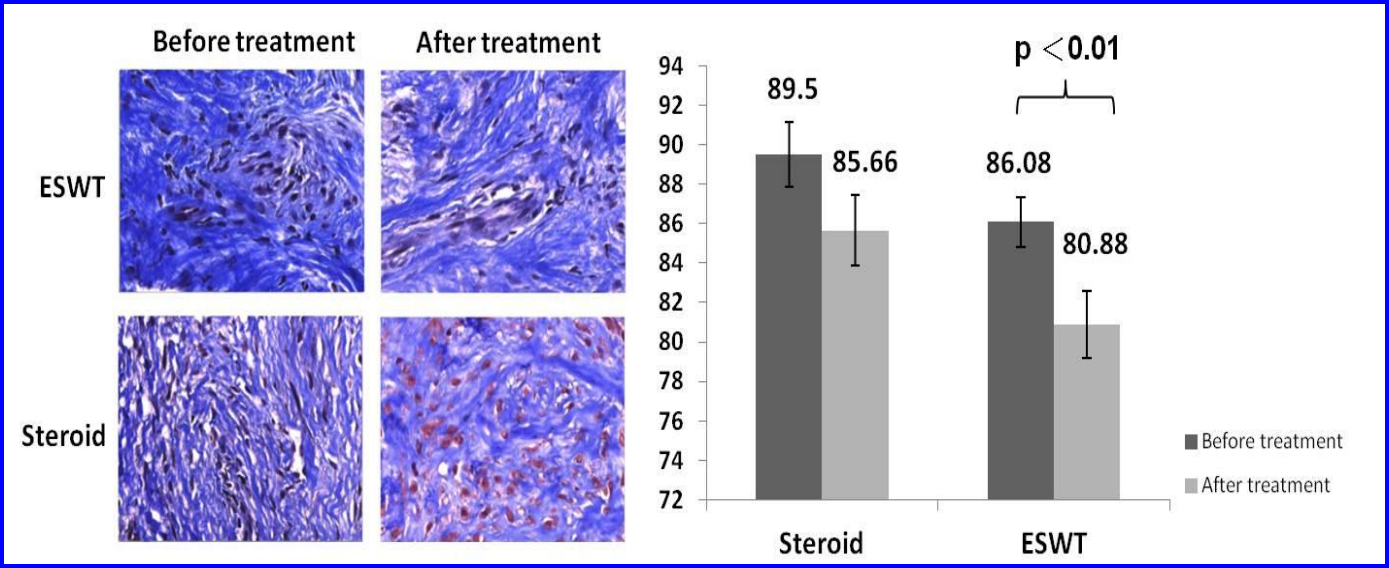
Collagen fibers

Collagen X

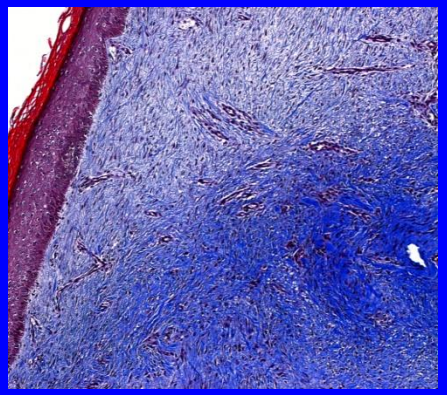


Collagen fibers

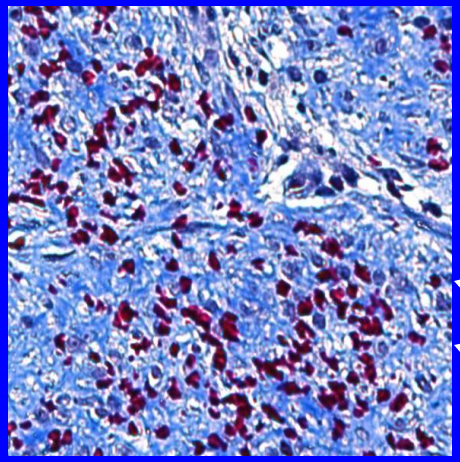
Masson's trichrome



Masson Trichrome Stain



Masson trichrome stain is a three-colour histochemistry stain.
Three dyes are employed selectively staining muscle, collagen fibers, fibrin, and erythrocytes.



Weigert's iron hematoxylin stains the nuclei in black, Biebrich scarlet-acid fuchsin stains cytoplasm and muscle fibers in red, and collagen is stained in blue with aniline blue.

Nuclei →black
Cytoplasm, muscle, erythrocytes →red
Collagen → blue

Collagen Contents in brief

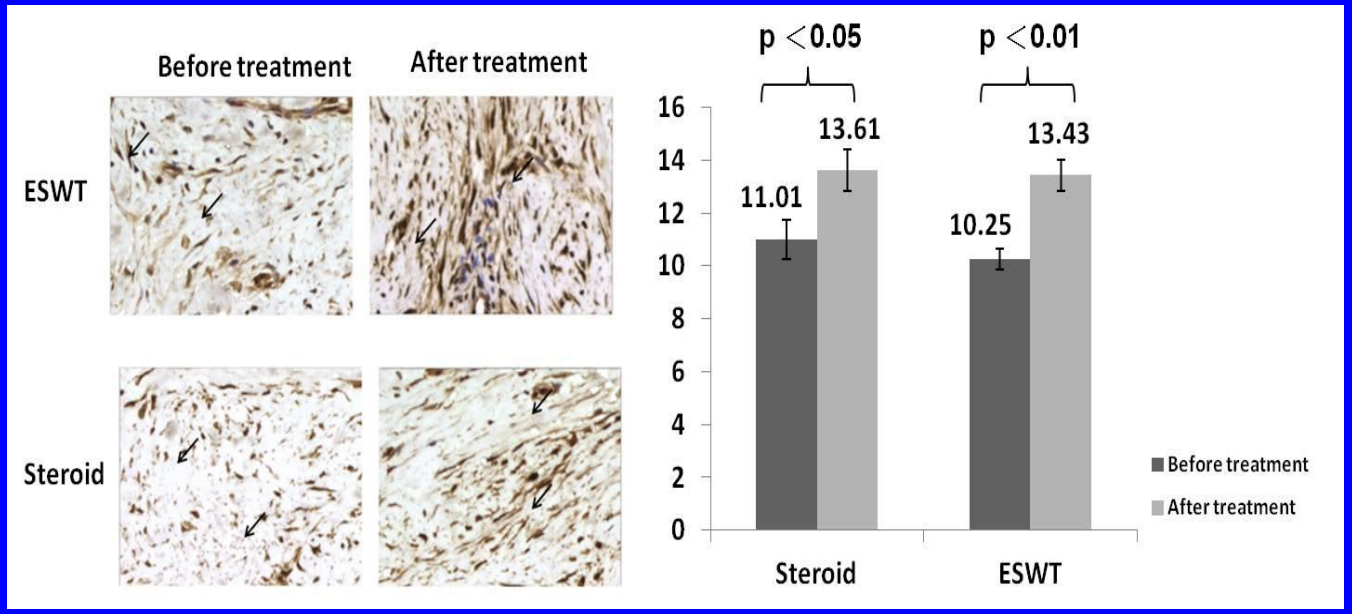
Significant decreases of collagen fibers type I, type III and Masson Trichrome stain were noticed after ESWT as compared to steroid injection. However, the differences of collagen contents between two groups were statistically not significant before and after treatment.

Immunohistochemical analyses

		Before treatment Mean±SD (Range)	After treatment Mean±SD (Range)	P-value[-1]
VEGF	ESWT (N=22)	33.27±11.22 (21-57)	36.84±11.31 (27-57)	0.299
	Steroid (N=17)	31.94±8.53 (21-47)	34.4±14.22 (23-61)	0.546
	P-value[-2]	0.274	0.497	
CD31	ESWT (N=22)	20.24±5.08 (9-27)	20.37±6.36 (9-32)	0.938
	Steroid (N=17)	19.54±4.41 (12-28)	19.78±5.11 (14-32)	0.88
	P-value[-2]	0.478	0.547	
TGF-β1	ESWT (N=22)	41.17±18.15 (24-74)	36.4±19.84 (16-76)	0.41
	Steroid (N=17)	37.63±16.84 (22-77)	29.31±11.24 (17-54)	0.1
	P-value[-2]	0.27	0.126	
IL-6	ESWT (N=22)	26.38±8.0 (18-57)	26.85±14.52 (11-67)	0.89
	Steroid (N=17)	27.44±11.25 (20-64)	22.83±8.49 (13-51)	0.186
	P-value[-2]	0.799	0.304	
PCNA	ESWT (N=22)	56.35±7.06 (52-72)	49.66±5.96 (38-60)	0.001
	Steroid (N=17)	44.99±13.48 (16-62)	41.26±13.83(11-63)	0.43
	P-value[-2]	0.058	0.063	
Fibronectin	ESWT (N=22)	25.53±3.22 (16-28)	18.73±3.53 (11-23	<0.001
	Steroid (N=17)	25.49±3.11(21-33)	49±3.61(16-30)	0.022
	P-value[-2]	0.127	0.959	
MMP-13	ESWT (N=22)	10.25±1.63(8-15)	13.43±2.47(9-19)	<0.001
	Steroid (N=17)	11.01±3.04(6-13)	13.61±3.27(7-18)	0.022
	P-value[-2]	0.418	0.846	
Caspase-3	ESWT (N=22)	30.83±8.8 (25-58)	38.16±13.43 (20-67)	0.038
	Steroid (N=17)	27.21±8.3 (17-50)	33.59±10.9 (21-56)	0.063
	P-value[-2]	0.081	0.673	
TUNEL	ESWT (N=22)	41.5±10.84 (28-71)	55.16±10.6 (37-81)	<0.001
	Steroid (N=17)	34.24±9.52 (11-42)	51.79±8.09 (42-64)	<0.001
	P-value[-2]	0.125	0.36	

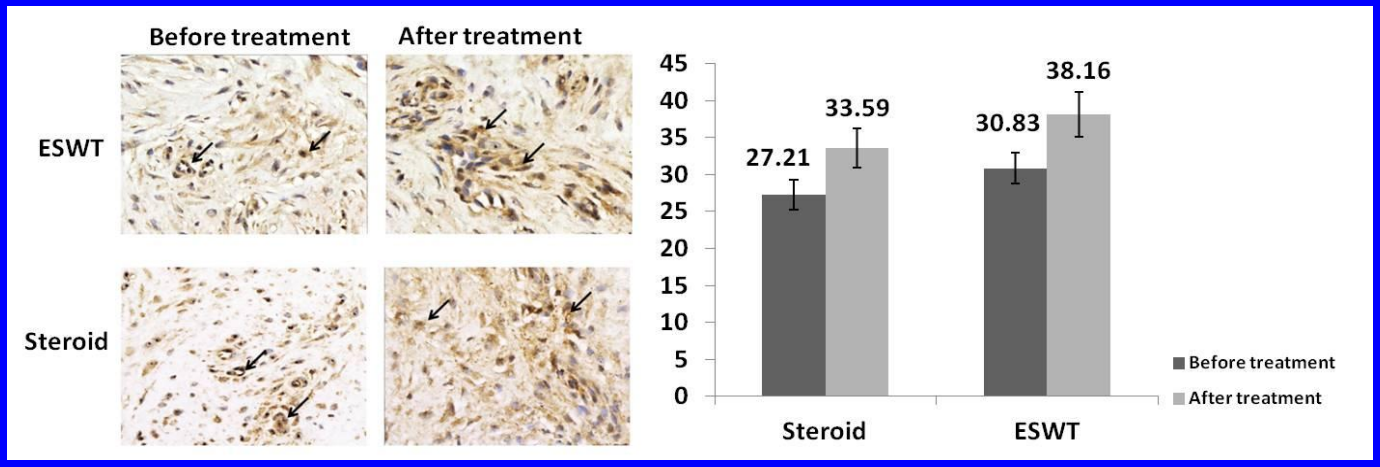
Collagen Degradation

MMP-13

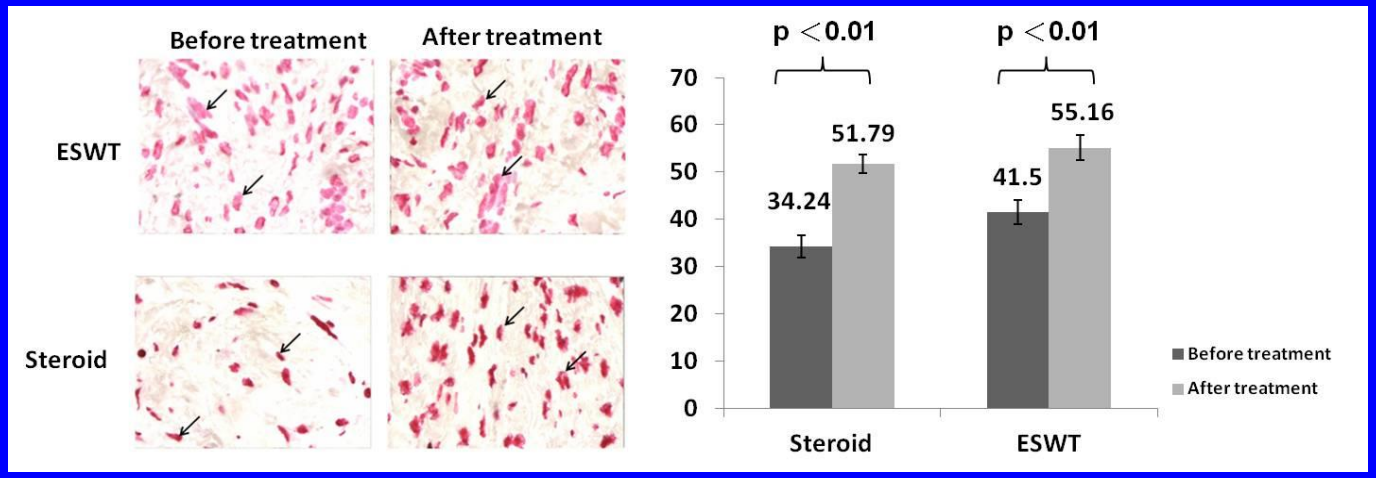


Apoptosis

Caspase-3

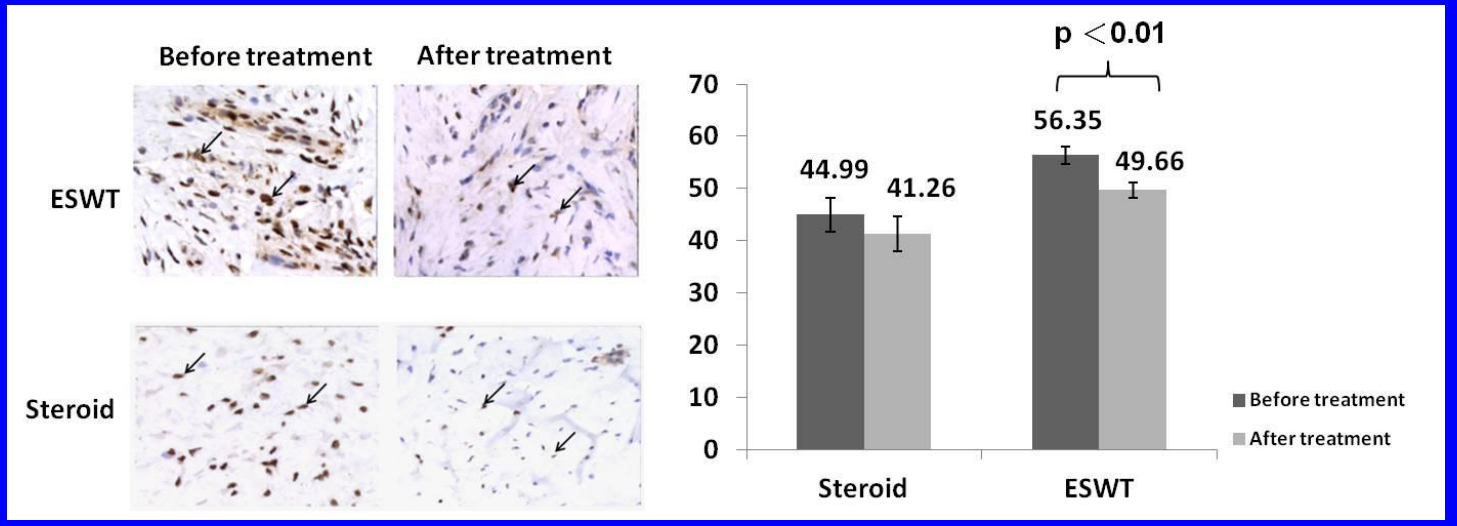


TUNEL

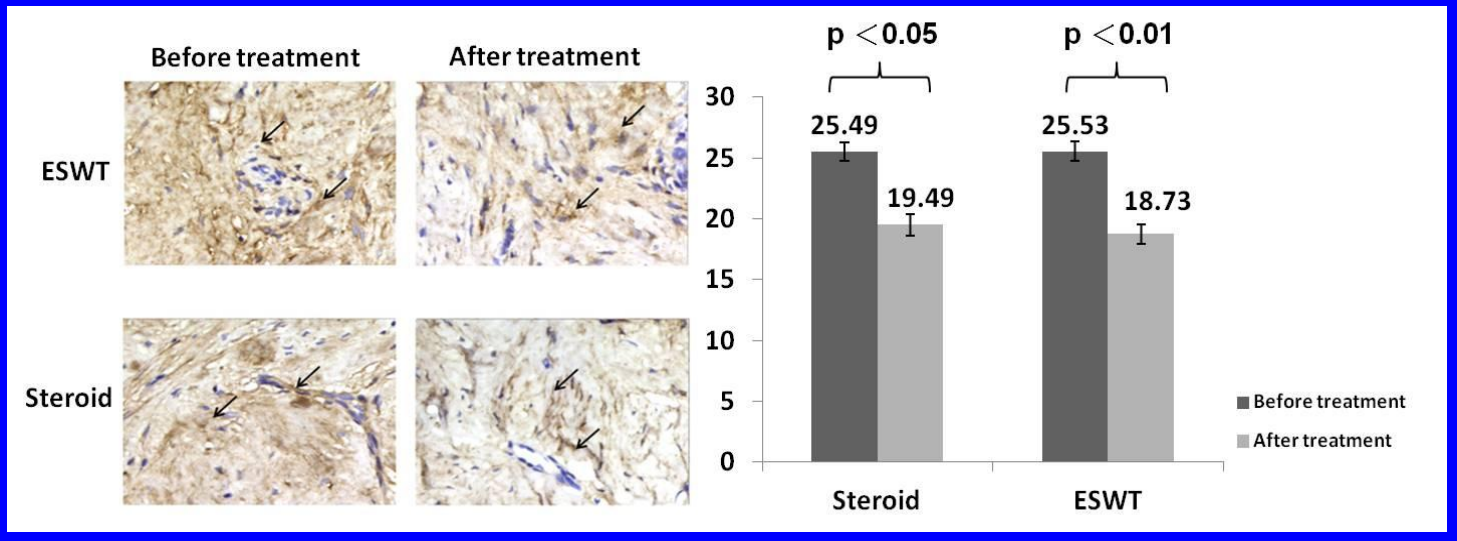


Proliferative

PCNA

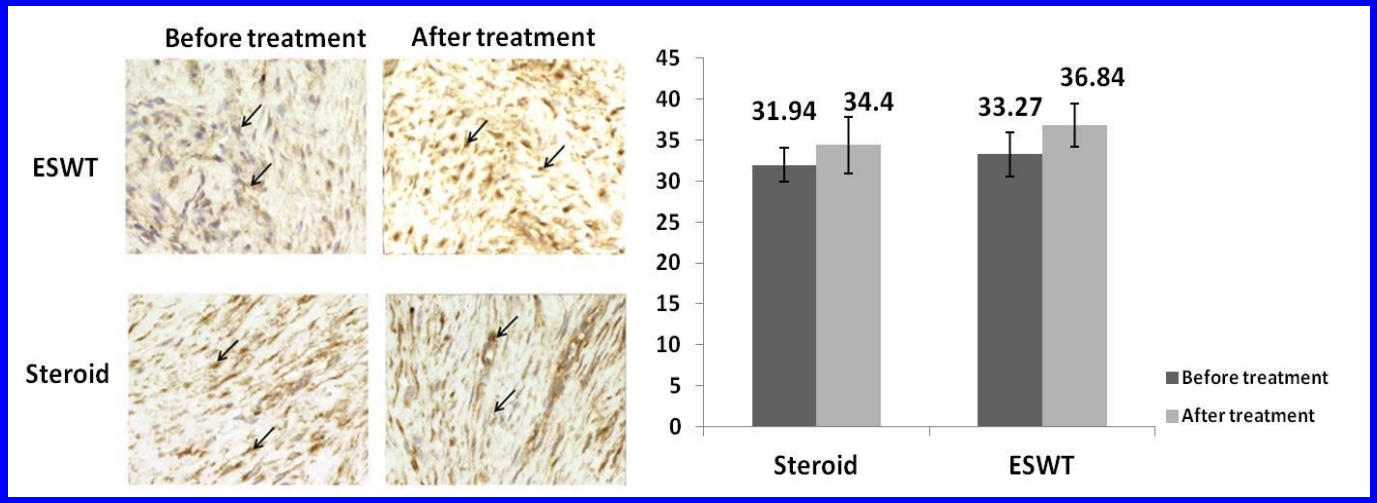


Fibronectin

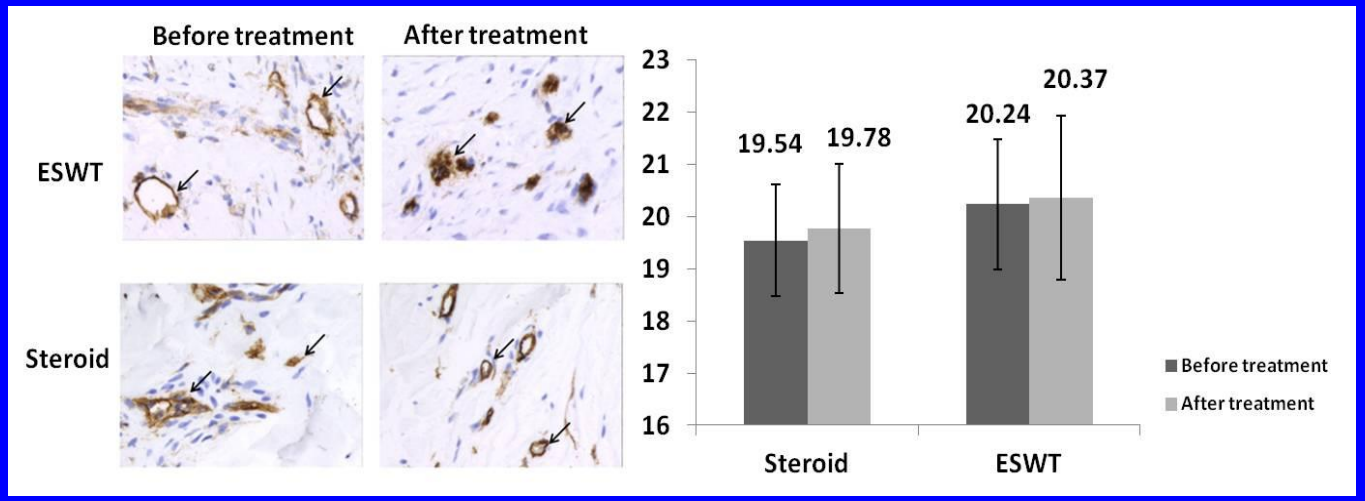


Angiogenesis

VEGF

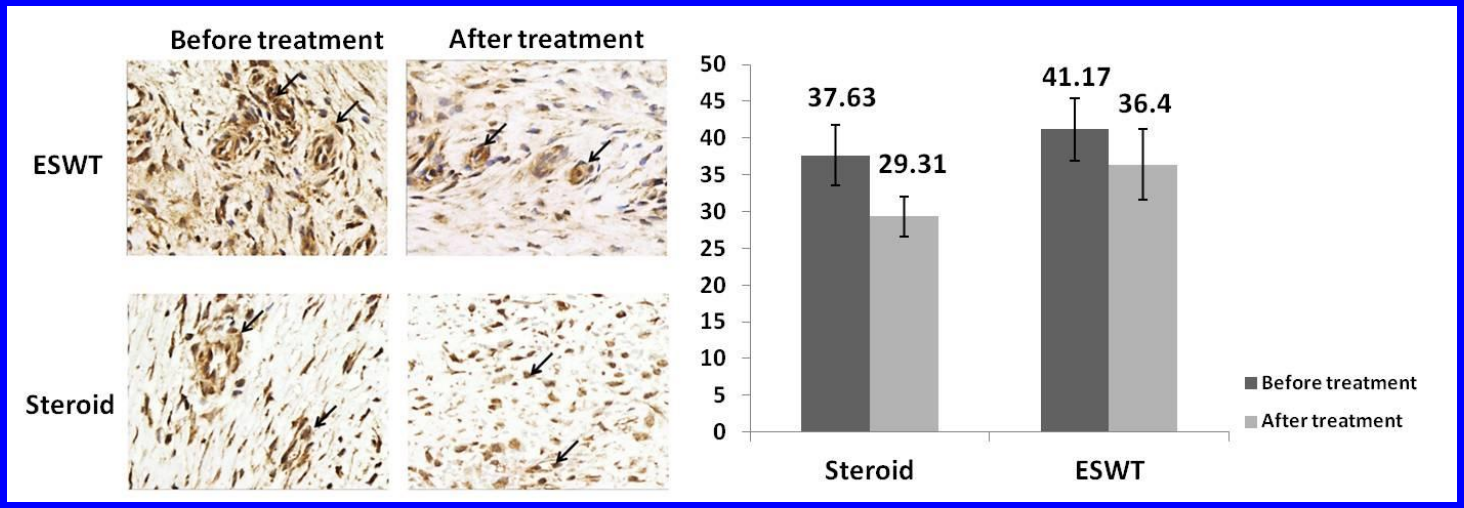


CD31

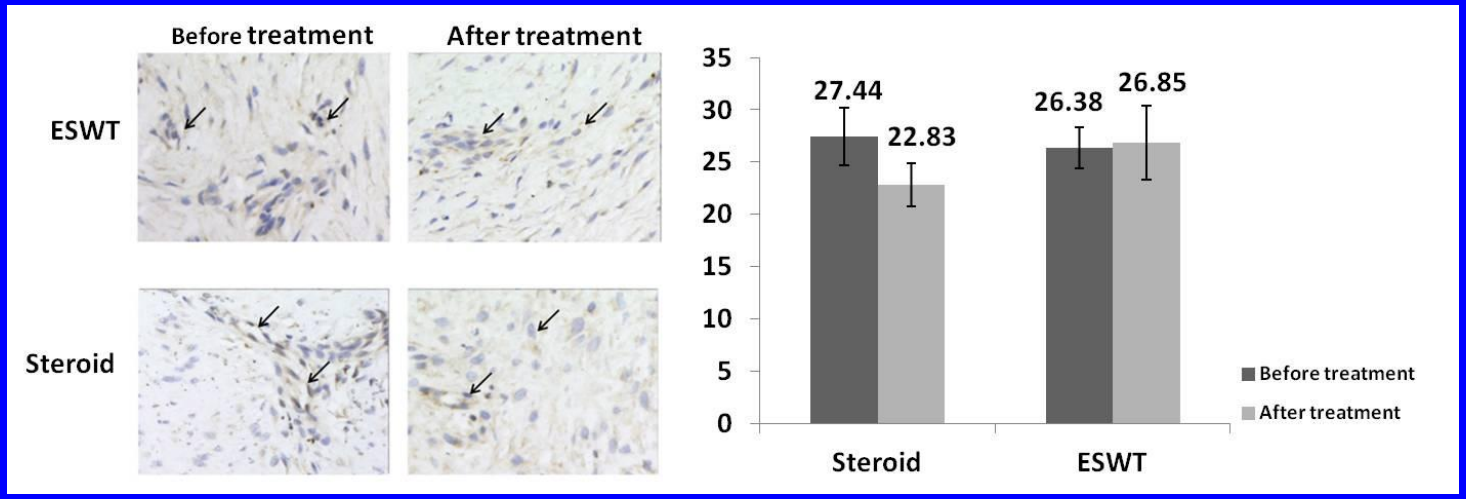


Anti-Inflammatory

TGF-β1



IL-6



Molecular Biomarkers in brief

Significant increases in degradation enzymes (MMP-13) and apoptotic biomarkers (caspase-3 and TUNEL) and decreases in proliferating fibronectin and PCNA were noticed after treatments with ESWT. However, the differences between two groups were statistically not significant before and after treatment ($P > 0.05$).

The angiogenic responses (VEGF and CD31) and the pro-inflammatory cytokines (TGF-β1 and IL-6) were relatively inert with low response in EWST for keloid scars.

Discussions (1)

Many methods of treatment were proposed for the keloids including steroid injection, surgical excision, radiation therapy, laser therapy, pressure therapy, cryotherapy, silicone gel, 5 flurourasil, 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 although intralesional injection with triamcinolone is considered the most effective.

Discussions (2)

The results of the current study demonstrated that ESWT is equally effective or better histologically as compared to steroid injection in treatment of keloid scars. The increase of MMP-13 induces collagen degradation and the keloid bundles become flatter. Most collagen contents (type I, type III and Masson Trichrome) were reduced after ESWT. It appears that ESWT primarily reduced collagen tissue formation in the treatment of keloid scars.

Conclusions

The results of the current study showed that ESWT is equally effective or better when compared to steroid injection in treatment of keloid scars. The complication rate was low after treatment with ESWT.

ESWT appears to inhibit collagen fiber formation by increasing enzyme degradation and apoptosis in keloid scars. ESWT may be used as the alternative method in the treatment of patients with keloid scars.