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Effect of extracorporeal shock wave therapy for burn scar regeneration: A prospective, randomized, double-blinded study

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ABSTRACT

Purpose: This study aimed to investigate the regeneration effect of extracorporeal shock wave therapy (ESWT) on hypertrophic scar regeneration using objective measurements.

Methods: This was a double-blinded, randomized, controlled trial of 48 participants who had undergone autologous split-thickness skin grafting (STSG) with same artificial dermis. The ESWT group ($n=25$) received shock waves with low-energy flux density (0.05–0.30 mJ/mm^2). The interval between treatments is a 1-week. The ESWT group also received recommended treatment. The control group ($n=23$) only received standard treatment. We measured skin characteristics before treatment and after 6 weeks for both groups.

Results: No significant intergroup difference was noted at the initial evaluations ($p>0.05$). The pre- to post-treatment change in the scar thickness ($p=0.03$) and erythema ($p=0.03$), greater reduction was found in the ESWT group than control group. The pre- to post-treatment change in the sebum level ($p=0.02$), more increase was found in the ESWT group. We found no significant differences in the change measurements between the two groups for melanin levels ($p=0.62$) and transepidermal water loss (TEWL) ($p=0.94$). The changes (skin distensibility, biological skin elasticity, gross skin elasticity, and skin viscoelasticity) measured with the Cutometer showed no significant differences between the two groups ($p=0.87$, $p=0.32$, $p=0.37$, and $p=0.29$, respectively).

Conclusion: This is the first report of ESWT on hypertrophic scar after burn using objective tools (melanin, erythema, sebum, TEWL, elasticity and thickness). ESWT has objective beneficial effects on burn-associated scar characteristics.

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1. Introduction

Although mortality rate has decreased due to the development of acute care in burn patients, the importance of chronic complications in terms of pain, pruritus, and esthetic aspects is increasing. On patients with partial or full-thickness burn injuries, autologous split-thickness skin grafting (STSG) are thought as the main treatment. Wound healing is a process for recovering the skin barrier, and involves a variety of cells [1]. Many studies showed that dermal fibroblasts generate hypertrophic scarring by upregulating fibroblast responses and extracellular matrix protein deposition [2]. Dermal elastic fibers are necessary for restoring skin quality, and decreased dermal remnants are present after STSG. Recovery of the dermis is important for healing process [3,4]. Laser treatment and medical needling are widely used in regenerative treatment as the effect of reorganizing the dermal layer [5,6]. Percutaneous collagen injection reinforces the endogenous potential for regeneration, with proliferating skin cells and dermal remodeling through the transforming growth factor (TGF)-β signal transduction pathway [7]. Although various therapeutic modalities have shown some efficacy, options remain limited in the treatment of hypertrophic scars.

Extracorporeal shock wave therapy (ESWT) has been used to treat musculoskeletal and neuropathic pain [8]. Recent research demonstrated ESWT stimulate some cell activities [9,10]. These results suggest that ESWT can induce the regeneration effects such as neoangiogenesis and anti-inflammation. Some studies on ESWT intimate some beneficial regeneration effects in burn wounds [11]. A study revealed that ESWT for the hypertrophic burn scar decreased scarring [9], while an investigation of burn scar contracture showed that ESWT improved scar appearance and pliability subjectively [12].

However, the regeneration effects of ESWT on hypertrophic scar qualities associated burns using objective measurements have not been evaluated clinically [13]. This project aimed to measure scar characteristics of the grafted skin with and without ESWL (thickness, elasticity, transepidermal water loss [TEWL], and erythema and melanin levels).

2. Subjects and methods

2.1. Study design and statement of ethics

This was a double-blinded, randomized controlled trial of 48 participants (41 male, 7 female) recruited from the Department of Rehabilitation Medicine, Hangang Sacred Heart Hospital, Korea, between March 2020 and May 2020. Our study was approved by the Ethics Committee of the Hangang Sacred Heart Hospital (HG2020-004), and registered in ClinicalTrials (NCT04340271). All participants provided written informed consent.

2.2. Study group

This study was included Korean burn participants who had undergone STSG using Matriderm® (MeSkin Solution Dr. Suwelack AG, Billerbeck, Germany) in Hangang Sacred Heart Hospital. The participants who were transferred to the Department of Rehabilitation Medicine at Hangang Sacred Heart Hospital were enrolled after complete epithelialization on scars that underwent skin grafting. Exclusion criteria were: those who had undergone STSG using other artificial dermis; wounds with spontanous epithelialisation; musculoskeletal diseases (degenerative joint diseases, rheumatoid arthritis, and fracture); scars with remaining open wounds; pregnancy; or potential for additional damage to the scars. To exclude drug effects as much as possible, standards for prescribed drugs were established as follows: participants taking steroids or retinoid-based drugs that could affect the skin were excluded

Fifty-six burn participants were randomly allocated using a computer program, to either ESWT (n=28) or Control (n=28) group. 3 participants in the ESWT group and 5 participants in the control group dropped out of the study for scheduling issues or undergoing post-treatment evaluations. Thus, 25 participants were included in the ESWT group and 23 participants in the Control group (Fig. 1).

2.3. Intervention

Subjects in both groups received standard treatment for burn scars, which comprised occupational therapy to improve upper limb function, physical therapy to improve lower limb function, stretching exercises for scar contracture, drugs for pain or pruritus caused by hypertrophic scar, pressure therapy, and moisturizing cream and silicone gel application. The researchers in this study conducted n ESWT in burn participants in the past [9,14,15]. In a previous study, the intensity and treatment intervals that were effective in burn participants were used. ESWT was conducted using the Duolith SD-1® device (StorzMedical, Tägerwilen, Switzerland), with an electromagnetic cylindrical coil source used to focus the shock wave (Fig. 2). ESWT was performed on treated scars, at an intensity of 100impulses/cm^2, an energy flux density (EFD) of 0.05 to 0.30mJ/mm^2, and frequency of 4Hz. Participants were treated with ESWT according pain tolerance to the body parts undergoing STSG with the same artificial dermis. ESWT was performed around the targetted sites at 100impulses/1cm^2 in accordance with a previous study [15]. With regard to volume of treatment, 1000 to 2000 impulses were administered per session, for 6 sessions held at 1-week intervals (Fig. 3). In the control group, standard treatment of burn scars except for ESWT was performed in the same manner as in the ESWT group.

2.4. Outcome measures

To evaluate the effect of ESWT, investigators compared the skin test results (thickness, melanin, erythema, TEWL, sebum, and skin elasticity levels) between the ESWT and control groups, from baseline measures immediately before the treatment and measures immediately after six weeks. Participants were made comfortable and acclimatized to room conditions. Room temperature was maintained at 20–25°C and relative humidity at 40–50%. In the supine position, skin properties were measured [16]. The thickness was measured

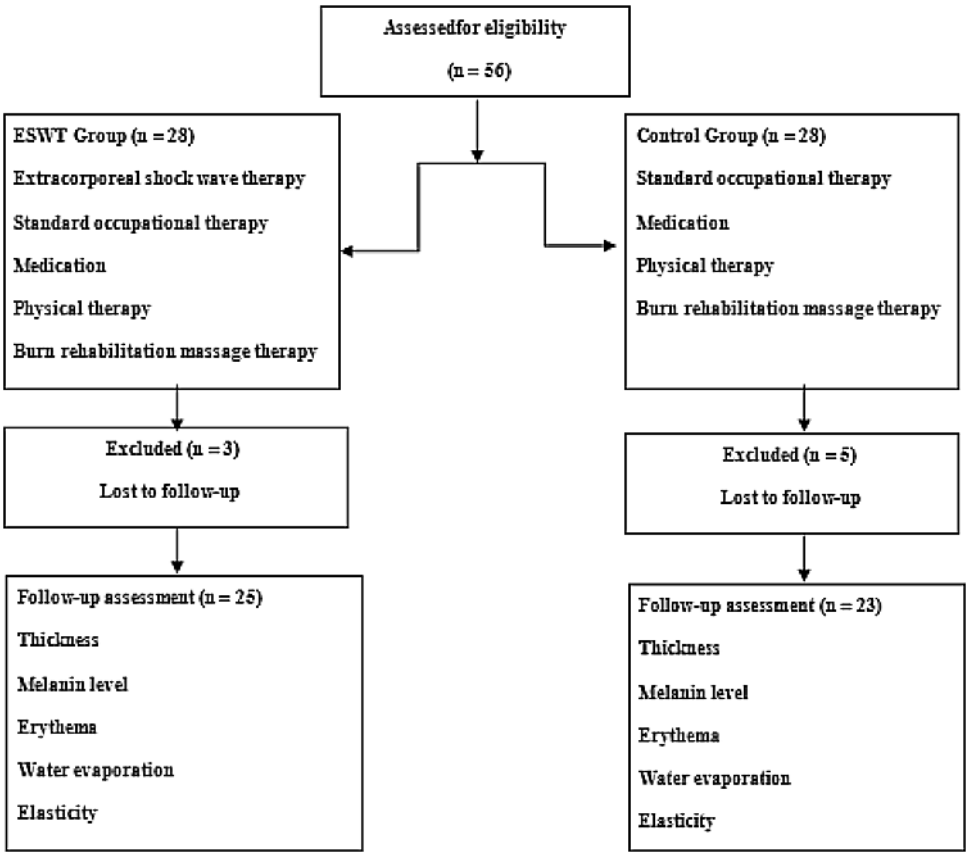

Fig. 1 – Diagram for subject enrollment, allocation and follow up.

with a ultrasonic wave equipment (128 BW1 Medison, Korea). Mexameter® (MX18, Courage-Khazaka Electronics GmbH, Germany) was used to measure melanin levels and the severity of erythema. The higher values indicating a darker and redder skin. Transepidermal water loss (TEWL) was measured with a Tewameter® (Courage-Khazaka Electronic GmbH, Germany), which is used for evaluating water evaporation. Sebum in the scars was measured with the Sebumeter® (Courage-Khazaka Electronic GmbH, Germany). The measurement is based on the principle of grease-spot photometry using a cassette with its special tape. A microprocessor calculates the result, which is shown on the display in μg/cm^2. Elasticity was measured using Cutometer SEM 580® (Courage-Khazaka Electronic GmbH, Cologne, Germany), which applies negative pressure (450 mbar) on the skin. The numeric values (mm) of the skin's distortion is presented as the elasticity. Two seconds of negative pressure of 450 mbar is followed by 2 s of recess, and this consists of a complete cycle. Three measurement cycles were conducted, and the average values were obtained [17] (Fig. 2). The parameters consist of the following biomechanical skin properties: distenstibility, elasticity, and viscoelasticity. Distensibility means the length of total displacement from initial postion at maximum negative pressure. Gross elasticity means the ability of the skin to return to its initial position following displacement. Biologic elasticity means the ratio of immediate retraction to total displacement. Viscoelasticity means the ratio of delayed distension of immediate distension. Outcome measurements and data analyses were performed by a trained and blinded outcome assessor who was not involved in the intervention. Possible complications (pain, ecchymosis, skin abrasion, and swelling) were observed.

2.5. *Statistical analysis*

The evaluated data were analyzed using SPSS version 23.0 (IBM, Armonk, NY, USA). Fisher's exact test was used to evaluate the homogeneity of the distribution of sex, burn mechanism, and body part of STSG between the two groups before treatment. The independent *t*-test was used to evaluate the homogeneity of the distribution of the age, TBSA, and TEWL after normality test. The Mann–Whitney test was used to evaluate the homogeneity of the distribution of the duration between injury and treatment, duration since STSG, pigmentation, erythema, sebum, skin distensibility, biologic skin elasticity, gross skin elasticity, and skin viscoelasticity after normality test. A between-group p-value <0.05 was deemed significant. The pre- to post-treatment scores were evaluated between the two groups using the Mann–Whitney for all parameters after normality test, with a p-value <0.05 deemed significant.

3. Results

Demographic characteristics were not significant different ($p>0.05$, all; Table 1). No significant intergroup difference was noted at the initial evaluation ($p>0.05$, all; Table 2).

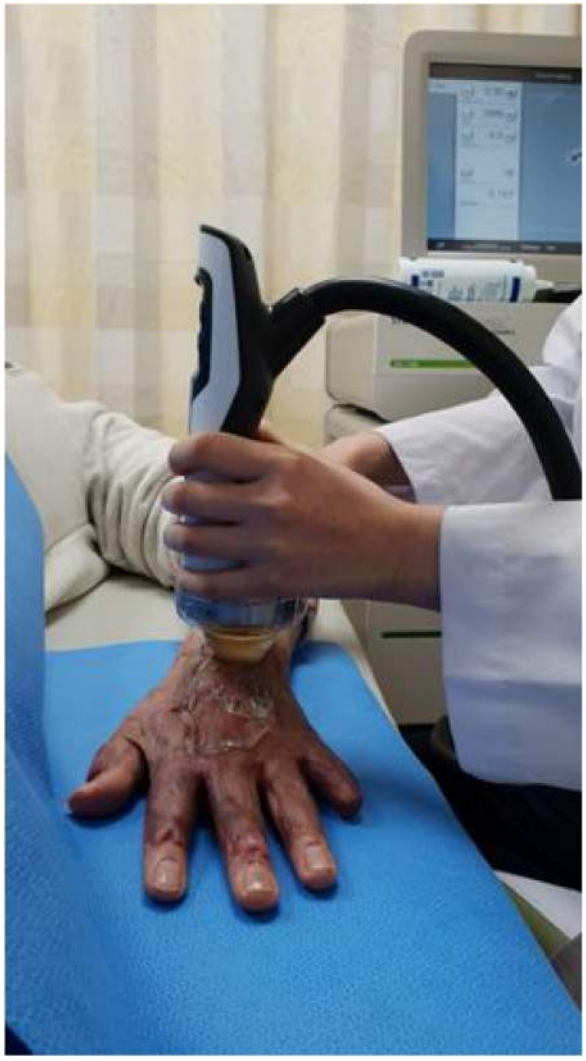

Fig. 2 – Extracorporeal shock wave therapy was administered to a burn patient. The administered shock wave dose was 100 impulses/cm^2 at 0.05 to 0.30 mJ/mm^2 with a total of 1000 to 2000 impulses.

We found improved changes (pre- to post-treatment) in scar thickness and erythema of the ESWT groups compared with the changes of the control group (p=0.03 and p=0.03). More changes in the scar thickness and erythema were found in the ESWT group (0.00±0.01 and −86.68±116.63) compared with changes of the control group (0.06±0.09 and −15.26 ±90.32) (Table 3). We also found significant changes in sebum levels in the ESWT group (71.32±84.65) compared with change of the control group (30.78±80.51) (p=0.02). However, we found no differences between groups in any of the other measurements, including melanin, TEWL, distensibility, or elasticity.

For the participants, some discomfort was mentioned during the treatment of ESWT, but no session was discontinued due to pain. No participants experienced adverse events such as ecchymosis, skin abrasion or worsening of swelling during ESWT.

4. Discussion

The purpose of this study was to explore the effects of ESWT for the management of hypertrophic scars. To evaluate the ESWT, comparison was limited to the scars which underwent STSG with the same artificial dermis. For managing the hypertrophic scar, ESWT had a positive effect on suppressing scar thickness, erythema, and sebum levels during the study period.

Wound healing can have good outcomes depending on homeostasis, inflammation, matrix synthesis, and tissue remodeling [18]. The mechanisms of hypertrophic scarring are persistent inflammation and fibroblast activation. Fibroblasts from hypertrophic scarring generate elevated collagen production [2]. TGF-β1 plays a major role in the genesis of fibroblasts during fibrosis in tissues [19]. ESWT on skin wound accelerates epithelialization by angiogenesis and the suppression of inflammation [20,21]. TGF-β1, collagen, and fibronectin levels were reduced after ESWT. Zhao et el. showed that shock wave therapy improved scar characteristics by interfering with the TGF-β1/Smad signaling pathway [22]. Many studies with ESWT investigated the potential to suppress fibrosis [23 –25]. These results demonstrate that ESWT is associated with suppression of some characteristics of hypertrophic scar [9,19]. This study provides further evidence in this regard.

The mechanisms of erythema after burn injury are explained by the locally intensified vascularization in the healing phase [5]. Many treatment techniques such as a botulinum toxin, laser treatment, and medical needling are known to improve erythema [5,6,26], but ESWT has a potential effect of improving blood circulation [27]. So the improvement of erythema observed in this study may have been through other mechanisms. In other studies, ESWT accelerated epithelialization associated with increased blood supply, perhaps through reducing inflammation in the healing process [28,29]. One study explained that ESWT works by breaking down the collagen fibers and remodeling scars [12,30]. Saggini et al. found that ESWT activates fibroblasts with deposition of thinner and parallel collagen [31,32]. In and *in vivo* study, ESWT produced a higher collagen content and a thicker epidermis and dermis compared to normal skin. ESWT during acute burn wound healing showed a higher re-epithelialization rate, more vessels, and faster development of a uniform layer of granulation [33]. ESWT is also associated with changes in skin protection, such as at the stratum corneum barrier [34,35]. Some studies have proposed that the cells in the sweat glands contribute to re-epithelialization by migrating upward and differentiating to repair skin wounds [36]. Studies regarding sebum found that differentiation and apoptosis of keratinocytes affect the lipid barrier in the epidermis [37,38]. The elevated lipid barrier levels increased along with keratinocyte differentiation. It was found that keratinocyte migration increased with ESWT treatment in chronic skin diseases [39]. After ESWT, dermal cells such as fibroblasts, endothelial cells, and hair follicle cells demonstrated a higher expression of fibroblast growth factor-2 associated with stimulation of the dermis without injury of the epidermis [32]. It was found that the erythema and sebum measurements from the epidermis and dermis were significantly improved in the ESWT group. This may be associated

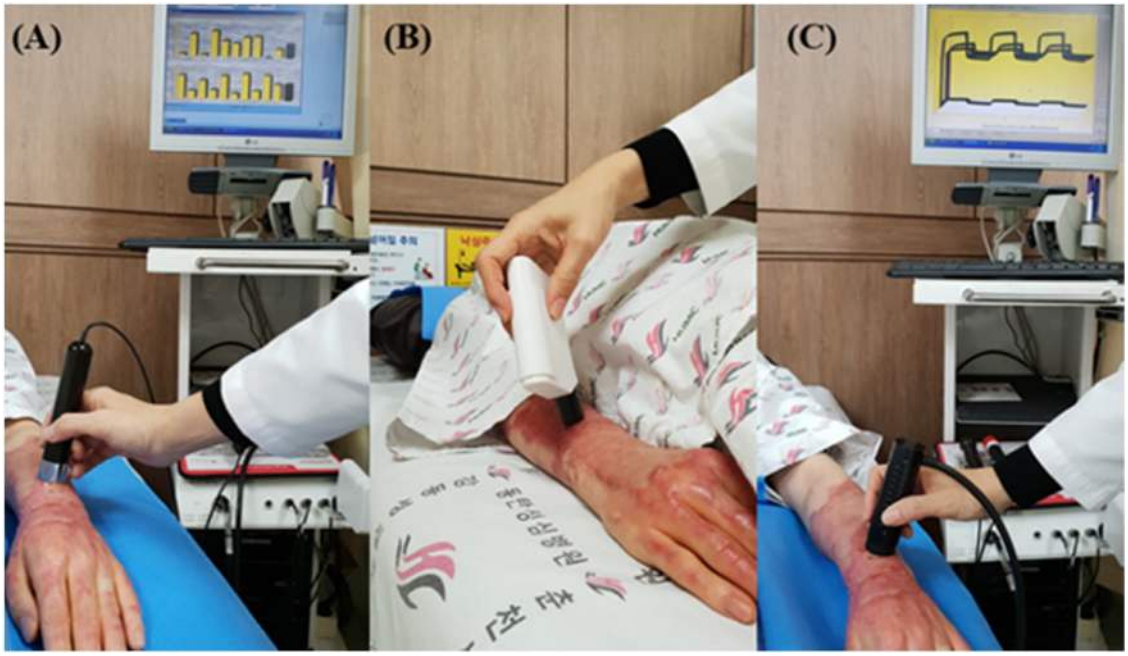

Fig. 3 – (A) Measurement of melanin levels and erythema using Mexameter® (MX18, Courage-Khazaka Electronics GmbH, Germany), (B) Measurement of sebum using Sebumeter® (Courage-Khazaka Electronic GmbH, Germany), (C) Measurement of elasticity using Cutometer SEM 580® (Courage-Khazaka Electronic GmbH, Cologne, Germany).

Table 1 – Participants characteristics.

	ESWT (n=25)	Control (n=23)	p
Male: Female, n	25: 2	18: 5	0.40
Age (years)	46.20±14.52	45.52±11.71	0.88
TBSA (%)	31.40±17.01	35.26±13.79	0.67
Body parts of STSG, (%)			0.87
Arms	2 (8)	2 (9)	
Forearms	8 (32)	10 (43)	
Hands	9 (36)	8 (35)	
Legs	6 (24)	3 (13)	
Mechanism of burn			0.73
Flame	17(68)	14(61)	
Electrical	5(20)	5(21)	
Scalding	3(12)	4(18)	
Duration (days) between the burn injury and treatment	69.16±30.96	65.65±20.31	0.99
Duration (days) since STSG	51.20±33.66	42.48±38.95	0.06

Values are presented mean±standard deviation or as numbers (%), TBSA=total burn surface area; STSG=split-thickness skin grafting.

Table 2 – Pre-homogeneity test of initial assessment.

	ESWT (n=25)	Control (n=23)	p
Thickness (cm)	0.19±0.07	0.18±0.05	0.86
Melanin (AU)	190.24±82.92	174.22±75.54	0.53
Erythema (AU)	504.40±108.79	490.26±102.10	0.26
TEWL (g/h/m^2)	17.24±5.50	15.65±5.61	0.16
Sebum (μg sebum/cm^2)	35.44±56.66	25.43±41.99	0.55
Skin distensibility	0.74±0.64	0.69±0.63	0.76
Biologic skin elasticity	0.42±0.25	0.39±0.26	0.73
Gross skin elasticity	0.58±0.31	0.63±0.21	1.00
Skin viscoelasticity	0.49±0.48	0.46±0.20	0.93

Values are presented as mean±standard deviation, ESWT=extracorporeal shock wave therapy, AU=arbitrary units, TEWL=transepidermal water loss.

Table 3 – Change score (pre- to post-treatment) on measured outcomes.

	ESWT (n=25)	Control (n=23)	p
Thickness (cm)	0.00±0.01	0.06±0.09	0.03*
Melanin (AU)	3.40±87.41	8.30±88.82	0.62
Erythema (AU)	−86.68±116.63	−15.26±90.32	0.03*
TEWL (g/h/m^2)	1.31±7.14	0.00±6.87	0.94
Sebum (μg sebum/cm^2)	71.32±84.65	30.78±80.51	0.02*
Skin distensibility	0.03±0.50	−0.13±0.67	0.87
Biologic skin elasticity	0.00±0.16	0.03±0.18	0.32
Gross skin elasticity	−0.02±0.20	−0.08±0.27	0.37
Skin viscoelasticity	0.01±0.44	0.07±0.16	0.29

Values are presented as mean±standard deviation, * $p<0.05$ between groups, *Mann–Whitney test, ESWT=extracorporeal shock wave therapy, AU=arbitrary units, TEWL=transepidermal water loss.

with the effect of ESWT on epidermal and dermal cell stimulation of hypertrophic scar tissue.

The mechanical function of the extracellular matrix depends on the architecture of the collagen. Collagen has a role on skin elasticity. The proteoglycan-rich matrix is necessary for maintaining skin viscous quality [40]. The dermis has to permit large elastic deformations and have a high tensile strength [40]. Distensibility is linked to collagen and elastic fibers stretching. Elasticity is related to the function of elastic fibers. Viscoelasticity is related to the displacement of interstitial fluid throughout the fibrous network and deformation [16]. The scar has little elasticity and distensibility because of an abnormal collagen pattern and alterations in the proteoglycans matrix [41]. *In vitro* ESWT improves elasticity due to tissue remodeling in chronic tendinopathy [13,42]. Distensibility is also related to the extent of fibers stretchings, but also to the thickness of the scar. It is thought that there are no significant changes in cutometer study as the thickness of the scars is increased due to the research conducted during proliferative phase in this study.

Most of our subjects were men, so there is limitation regarding the generalizability. The small sample size may have masked some statistical results. For detailed information, the Vancouver scar scale could be analyzed. However, the Vancouver scar scale was not included in the routine scar evaluations in this study. Further study is also required to observe the changes of scar characteristics combined with a longer time frame, and psychometrics measurements. Additional studies regarding ESWT protocols(intensity, frequency, and interval) are necessary. In order to confirm the mechanisms of the effects on the scar characteristics observed in this study, future cellular and molecular studies are essential.

5. Conclusions

This study is the first report to compare and analyze ESWT for hypertrophic scars in burn patients who underwent STSG using the same artificial dermis. In this study, we showed that scars can be reliably measured using objective tools (scar thickness, erythema, and sebum) in a human research. This will provide further essential information that can help improve the management on hypertrophic scars. ESWT can be one of the modalities for improving scar characteristics.

Conflicts of interest

The authors declare no potential conflict of interest.

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