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The clinical utility of extracorporeal shock wave therapy for burn pruritus: A prospective, randomized, single-blind study

So Young Joo, Yoon Soo Cho, Cheong Hoon Seo *

Department of Rehabilitation Medicine, Hangang Sacred Heart Hospital, College of Medicine Hallym University, Seoul, Republic of Korea

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ABSTRACT

Purposes: To investigate the effect and mechanisms of extracorporeal shock wave therapy (ESWT) on burn scar pruritus.

Methods: Forty-six patients participated (experimental group, n=23; sham stimulation group, n=23). Patients had complaints of severe pruritus ranging from 5 to 10 on the visual analog scale. The experimental group received 1000–2000 shock waves for each treatment with 100 impulses/cm^2, each with low-energy flux density (0.05–0.20 mJ/mm^2) and a 1-week interval between treatments for 3 weeks. The numerical rating scale (NRS), 5D-Itch Scale, and Leuven Itch Scale were evaluated immediately before ESWT and after the third session. Laser Doppler blood perfusion imaging (LDI) was performed immediately before ESWT and after the first and third sessions.

Results: In the experimental group, mean NRS scores were 6.30 ± 1.29 before therapy and 3.57 ± 2.09 after the third session, and the difference was significant ($p < 0.001$). NRS scores in the experimental group after the third ESWT were significantly decreased compared to those of the sham stimulation group ($p = 0.009$). The duration, severity, and consequences scores of pruritus on the Leuven Itch Scale after the third ESWT were significantly decreased in the experimental group compared with the sham stimulation group ($p = 0.033$, $p = 0.007$, and $p = 0.009$, respectively). The direction score on the 5-D Itch Scale after the third ESWT was significantly decreased in the experimental group compared to the sham stimulation group ($p = 0.033$). After the first ESWT session and after 3 sessions, the burn area had a significant increase in perfusion according to LDI, compared with the scores before treatment in the experimental group ($p = 0.023$ and $p = 0.013$, respectively).

Conclusion: ESWT is a non-invasive modality that significantly reduced burn-associated pruritus.

Abbreviations: ESWT, extracorporeal shock wave therapy; NRS, numerical rating scale; LDI, Laser Doppler blood perfusion imaging; SP, substance P; CNS, central nervous system; LIS, Leuven Itch Scale; CGRP, calcitonin gene-related peptide.

* *Corresponding author at*: Department of Rehabilitation Medicine, Hangang Sacred Heart Hospital, Hallym University, 94-200 Yeongdeungpo-Dong Yeongdeungpo-Ku, Seoul, 150-719, Republic of Korea. Fax: +82 2 2635 7820.
E-mail address: chseomd@gmail.com (C.H. Seo).

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1. Introduction

It is challenging to define burn pruritus because its mechanisms are not well defined. Burn scar pruritus can be defined as an urge to scratch a burn wound during the healing process. On discharge from the hospital, the incidence of pruritus is reported to be 87% [1]. Complaints of acute pruritus begin within several days of the burn injury, and chronic pruritus may continue for up to 2 years after healing. Pruritus is a quality of life problem for burn patients. It disrupts patients' sleeping and leisure activities. In most burn centers, antihistamines used as first-line treatment for pruritus in patients with burns. However, a study assessing the efficacy of several antihistamines in burn patients with pruritus showed that complete relief of pruritus was accomplished in only 20% of patients [1]. Histamine is one of the pruritogenic mediators. It is released in tissues with acute inflammation and in granulation tissue that has formed. These pruritogenic mediators activate C fibers, and the impulses of pruritus are transmitted to the spinal cord. Other mediators of pruritus are neuroinflammatory transmitters, including substance P (SP) released by mast cells. C fibers transmit impulses to the dorsal root ganglion and central nervous system (CNS) [2,3]. Some studies have reported that chronic pruritus, which is unresponsive to histamines, can be explained by neuropathic mechanisms based on its response to gabapentin. Gabapentin is able to control pruritus by virtue of its ability to inhibit hypersensitivity reactions after nerve injury and by its secretion of inhibitory neurotransmitters. Thus, it has been suggested that the CNS is involved in the development and maintenance of pruritus, and neuropathic mechanisms have similar patterns to sensitization in neuropathic pain models. Pruritus is considered a form of pain, and the current practices for management of pruritus, such as emollient cream and pharmacological or physical therapies, have shown limited benefits. Standard treatment protocols for pruritus have not been established, and new treatment approaches are being researched.

Extracorporeal shock wave therapy (ESWT) has been used to treat musculoskeletal diseases (plantar fasciitis, lateral epicondylitis of the elbow, etc.). Recent research has demonstrated the effectiveness of ESWT in stimulating biological activities that involve intra-cell and cell-matrix interactions [4]. These results suggest that ESWT can be used in tissue regeneration. The concept of tissue regeneration is associated with neoangiogenesis and anti-inflammation [5,6]. Recent mechanistic research studies of ESWT have demonstrated angiogenetic and anti-inflammatory effects in ischemic skin flaps and acute burn wounds.

The incidence of burn-associated pruritus indicates the need for another modality that can positively reduce pruritic symptoms. The purposes of this study were to determine the effect of ESWT for the management of refractory burn scar pruritus and to clarify its mechanisms of ESWT in burn scar pruritus via Laser Doppler blood perfusion imaging.

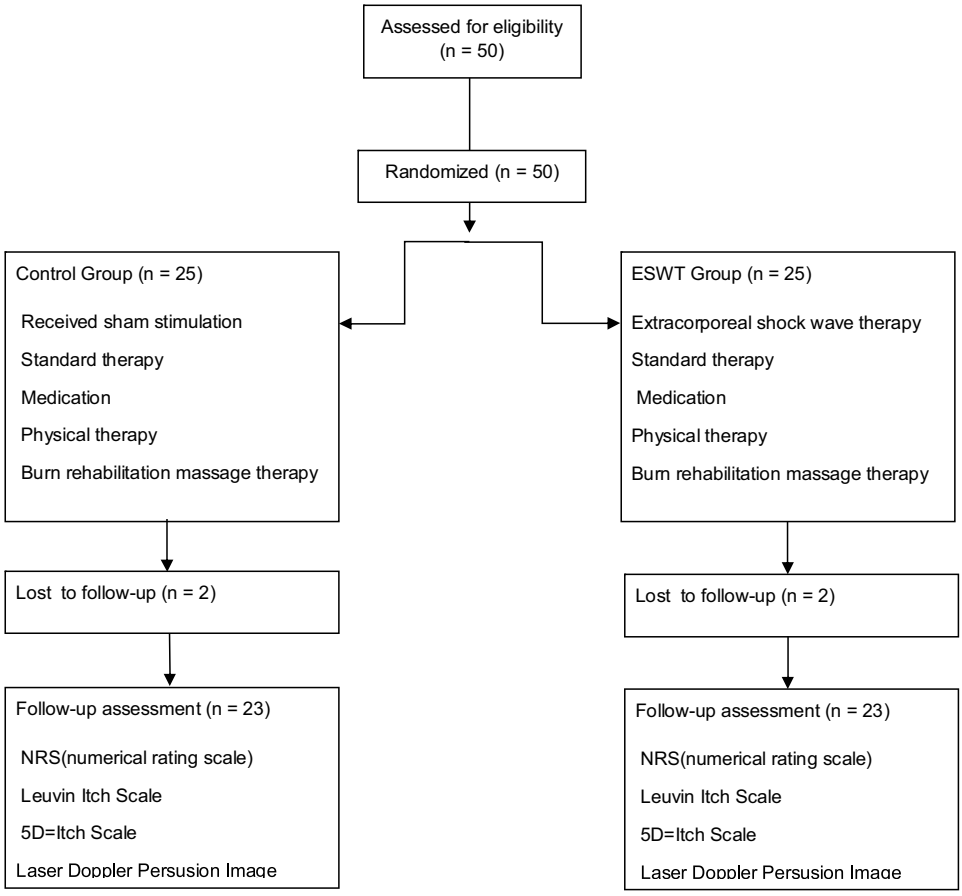

Fig. 1 – Diagram for subject enrollment, allocation and follow up.

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2. Patients and methods

Adult patients with partial-to-full-thickness burns that had spontaneously healed or underwent skin grafting were enrolled. Forty-six patients from the Department of Rehabilitation Medicine at Hangang Sacred Heart Hospital in Korea between June 2015 and February 2017 were recruited to participate in this study. Our study was approved by the Ethics Committee of the Hangang Sacred Heart Hospital. Patients provided written informed consent. Study patients had severe pruritus with a rating of at least 5 on the numerical rating scale (NRS), despite being treated with drugs and physical therapy for more than 1 week after admission to the Department of Rehabilitation Medicine. Inclusion criteria were as follows: man or woman between 18 and 75 years old; patients with partial or full-thickness burns that healed spontaneously or underwent skin grafting; and those with a complaint of severe pruritus with a rating of 5–10 on the NRS. Patients were excluded if they had a history of cancer, pathologic fracture, burns located on the genitalia, pregnancy, or if there was potential for additional damage to the skin due to the use of ESWT. Numbers were assigned to patients according to the order of admissions of 50 burn patients with pruritus who satisfied all the aforementioned criteria. Then a computer program was used to divide them into the experimental group (n=25) or sham stimulation group (n=25). Two patients each in the sham stimulation group and experimental group dropped out of the study because they did not want to undergo serial assessments. Thus, patients were randomly divided into two groups (23 subjects each) (Fig. 1). The two groups received the standard treatment, which involved medication, scar lubrication, burn rehabilitation massage therapy, and physical therapy. The experimental group was treated with ESWT. Patients in the experimental group were instructed to select the most pruritic area for the treatment. ESWT was conducted using the Duolith SD-1® device (Storz Medical, Tägerwilen, Switzerland) with an electromagnetic cylindrical coil source for the focused shock wave (Fig. 2). ESWT was performed around the primary treatment site at 100 impulses/cm^2, an energy flux density of 0.05–0.20 mJ/mm^2, and frequency of 4 Hz, and 1000–2000 impulses were administered at 1-week intervals for 3 sessions. In the sham stimulation group, the same shock wave equipment used in the experimental group was used with a sham adapter that had the same shape but emitted no energy.

To assess the effect of treatment, the NRS was used to evaluate the degree of subjective pruritus immediately before ESWT and immediately after the third session. Zero (0) represented no pruritus and 10 represented unbearable symptoms enough to produce bleeding. The 5-D Itch Scale [7], a subjective and multi-dimensional measure of the degree, duration, direction of improvement, disability, and distribution area of pruritus, was used. Each item was rated from 1 to 5 points according to the degree of pruritus, and the total score was calculated to quantify the pruritus. A total score of 5 indicated no pruritus, whereas a total score of 25 indicated the most severe pruritus. It is worth noting that the 5-D Itch Scale has been found to provide no validity

Fig. 2 – The extracorporeal shock wave therapy was administered to burn patients. The administered shock wave dose was 100 impulses/cm^2 at 0.05 to 0.20 mJ/mm^2 with a total of 1000–2000 impulses.

or reliability regarding the distribution domain for patients with burn because distribution-related items are limited to those in the burn areas; therefore, the distribution categories were not compared in this study [7]. The degree to which pruritus interfered with daily activities was measured using the Leuven Itch Scale (LIS) [8], which considers measurements of patients' subjective pruritus symptoms and their experience with pruritus treatment. The LIS scores evaluate pruritus frequency, duration, severity, as well as consequences (e.g., scratched skin regions and sleep disturbance). Each item, except for pruritus severity, was rated on a scale of 0–4. Pruritus frequency was scored as 0, 1, 2, 3, or 4, which corresponds to 0, 25, 50, 75, or 100 points, respectively. Pruritus duration was scored as 0, 1, 2, or 3, which corresponds to 0, 33.33, 66.66, or 100 points, respectively. Pruritus severity and pruritus distress were based on the measured scores. Pruritus consequences were scored as 0, 1, 2, 3, or 4, which corresponds to 0, 25, 50, 75, or 100 points, respectively. The location of pruritus was scored by aggregating the scores for all pruritic areas. Initially, each patient was acclimatized to 23 °C in a climate controlled room. Immediately before and immediately after the first and after third sessions, we performed Laser Doppler blood perfusion imaging (LDI) (Periscan PIM II®, Perimed, Stockholm, Denmark) which combines Laser Doppler and scanning to assess any changes in perfusion (Fig. 3). LDI [9] represents one of the more feasible methods for accurately determining the perfusion levels. Regions of interest were defined as 2 × 2 cm. Mean perfusion units were measured.

Statistical analysis was performed using SPSS, version 23 (IBM Corp., Armonk, NY, USA). To examine the pretreatment homogeneity between the experimental group and sham stimulation group, the Pearson chi-square, Fisher exact, independent t-test, and Mann–Whitney test were used, with

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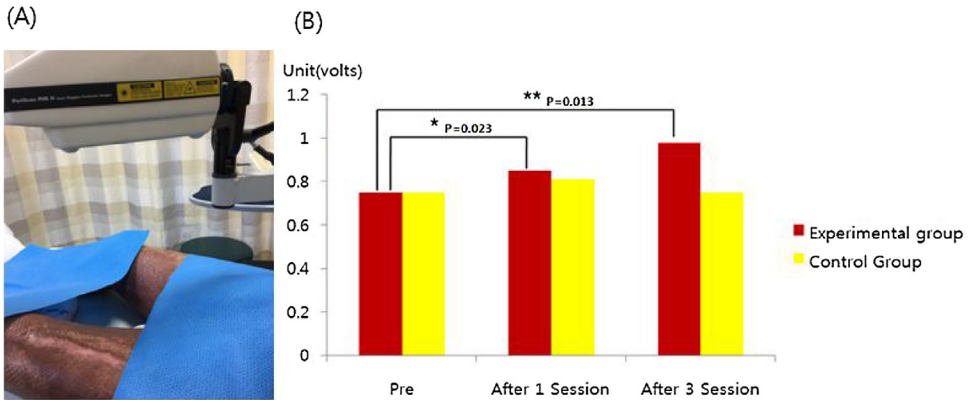

Fig. 3 – (A) Measurement of perfusion unit using Laser Doppler Blood Perfusin Imager (Periscan PIM II®, Stockholm, Denmark). (B) Perfusion units of the ESWT experimental group compared to the control group using the Laser Doppler Imager.

a significance level of $p<0.05$. Pretreatment scores were compared with post-treatment scores using the Wilcoxon signed-rank sum test and paired t-test, with a significance level of $p<0.05$. To determine the interaction effects of group and time (group × time) of perfusion units of LDI between the two groups, repeated-measure analysis of variance was used. Values are presented as a mean ± standard deviation.

3. Results

Forty-six patients completed the study in accordance with the study protocol. Patients' demographic characteristics (gender, age, total burn surface area, mechanism of the burn, type of treatment, duration from the burn injury to ESWT, and location of the burn) were similar between the two groups with no significant differences ($p>0.05$) (Tables 1 and 2).

The measured NRS scores in the experimental group and sham stimulation group decreased significantly from before ESWT to after the 3 sessions ($p<0.001$ and $p=0.002$, respectively) (Table 3). The difference in NRS scores between the experimental and sham stimulation group after 3 sessions was statistically significant ($p=0.009$) (Table 4). Thus, burn scar pruritus was reduced more significantly in the experimental group than in the sham stimulation group.

Mean scores on the 5-D Itch Scale (duration and degree of pruritus, direction of pruritus improvement, as well as

Table 1 – Demographic data.

	ESWT	Control	p
Male:Female	17:6	17:6	1.00[a]
Age (years)	45.44 ± 13.77	43.00 ± 10.03	0.50[c]
TBSA (%)	20.91 ± 15.18	21.17 ± 14.91	0.95[c]
Mechanism of burn n (%)			0.13[b]
Flame burn	10 (43)	13 (56)	
Electrical burn	3 (13)	3 (13)	
Contact burn	3 (13)	0 (0)	
Scalding burn	4 (17)	7 (30)	
Chemical burn	3 (13)	0 (0)	
Type of treatment n (%)			
Skin graft	17 (74)	18 (78)	0.74[a]
Duration (days) between burn injury and therapy	84.22 ± 58.62	74.09 ± 48.92	0.50[d]
Body parts of pruritus, n (%)			0.53[b]
Arms, thigh	11 (47)	11 (47)	
Forearm, leg	4 (17)	1 (4)	
Hand, foot	1 (4)	2 (8)	
Trunk, chest	7 (30)	8 (34)	
Face	0 (0)	1 (4)	

TBSA = total burn surface area, SB = scalding burn, FB = flame burn, CoB = contact burn.
Values are mean ± standard deviation.
[a] Pearson chi-square test.
[b] Fisher exact test.
[c] Independent t-test.
[d] Mann-Whitney test.

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Table 2 – Pre-homogeneity test of preliminary assessment.

	ESWT Before therapy	Control Before therapy	p
NRS	6.30±1.29	6.87±1.32	**0.14**[b]
5-D pruritus scale			
Duration	1.96±1.87	2.00±1.17	**0.85**[b]
Degree	3.52±0.79	3.48±0.73	**0.60**[b]
Direction	4.17±0.83	4.21±0.90	**0.80**[b]
Disability	3.30±1.15	3.21±1.04	**0.58**[b]
Leuven Itch Scale			
Frequency	78.26±18.93	79.35±12.28	**0.93**[b]
Duration	33.00±34.47	45.91±34.09	**0.18**[b]
Severity	63.04±12.95	68.70±13.25	**0.14**[b]
Consequences	32.51±21.50	37.85±23.39	**0.46**[a]
Laser Doppler (unit)	0.75±0.25	0.75±0.23	0.98[a]

Values are mean±standard deviation.
[a] Independent t-test.
[b] Mann–Whitney test.

disability) after 3 sessions significantly decreased compared with those before ESWT in the experimental stimulation group (1.96–1.39 points, p=0.046; 3.52–2.52 points, p<0.001; 4.17–2.78 points, p<0.001; and 3.30–2.35 points, p=0.004, respectively) (Table 3). Mean scores on the 5-D Itch Scale (degree and direction of pruritus) after 3 sessions significantly decreased compared with those before stimulation in the sham stimulation group (3.48–2.96 points, p=0.017 and 4.21–3.48 points, p=0.028, respectively) (Table 3). Scores of the direction of pruritus improvement in the experimental group were significantly reduced compared with those in the sham stimulation group after 3 sessions (p=0.033). Although the scores for duration, degree, and disability of pruritus decreased in both groups after 3 sessions, the differences between the groups were not significant (p=0.49, p=0.15, and p=0.17) (Table 4). However, the treatment results were improved in the experimental group compared to the sham stimulation group.

Mean LIS scores (pruritus frequency, duration, and severity, as well as consequences) after 3 sessions decreased compared with those before ESWT in the experimental group (78.26–67.39 points, p=0.075; 33.00–20.09 points, p=0.12; 63.04–35.22 points, p<0.001; and 32.51–17.19 points, p<0.001, respectively)(Table 3). Mean LIS scores after 3 sessions decreased compared with those before stimulation in the sham stimulation group (79.35–72.83 points, p=0.107; 45.91–43.04 points, p=0.79; 68.70–53.48 points, p=0.002; and 37.85–32.60 points, p=0.20) (Table 3). Statistically significant reductions were observed in pruritus severity and consequences scores of the experimental stimulation group (p<0.001 and p<0.001, respectively) and in severity scores of the sham stimulation group (p=0.002) after 3 sessions. Scores for duration, severity, and consequences of pruritus after 3 sessions in the experimental group were significantly reduced compared with those in the sham stimulation group (p=0.033, p=0.007, and p=0.009, respectively). Although the scores for frequency decreased in the experimental group after 3 sessions, the difference was not significant (p=0.42) (Table 4); however, the burn scar pruritus was improved in the experimental group compared to the sham stimulation group after 3 sessions.

After one ESWT session (p=0.023) and 3 sessions (p=0.013), the burn area had a significant increase in perfusion according to LDI, compared with the scores before treatment in the experimental group. In the sham stimulation group, differences between before therapy and after one session or 3 sessions were not significant (Fig. 3). Patients tolerated ESWT well without any adverse side effects; we observed no bleeding, hematoma, seroma, petechiae, or infection.

Table 3 – The changes in numerical rating scale (NRS), 5-D pruritus scale, Leuven Itch Scale.

	ESWT		p	Control		p
	Before therapy	After 3rd therapy		Before therapy	After 3rd therapy	
NRS	6.30±1.29	3. 57±2.09	**<0.001**[*]	6.87±1.32	5.35±2.31	**0.002**[a]
5-D pruritus scale						
Duration	1.96±1.87	1.39±0.66	**0.046**[*]	2.00±1.17	1.65±1.07	**0.118**[a]
Degree	3.52±0.79	2.52±0.59	**<0.001**[*]	3.48±0.73	2.96±0.93	**0.017**[a]
Direction	4.17±0.83	2.78±0.90	**<0.001**[*]	4.21±0.90	3.48±1.08	**0.028**[a]
Disability	3.30±1.15	2.35±1.23	**0.004**[*]	3.21±1.04	2.87±1.18	**0.057**[a]
Leuven Itch Scale						
Frequency	78.26±18.93	67.39±23.15	**0.075**[*]	79.35±12.28	72.83±19.81	**0.107**[a]
Duration	33.00±34.47	20.09±25.83	**0.12**[*]	45.91±34.09	43.04±37.80	**0.79**[a]
Severity	63.04±12.95	35.22±20.20	**<0.001**[*]	68.70±13.25	53.48±23.08	**0.002**[a]
Consequences	32.51±21.50	17.19±16.24	**<0.001**[b]	37.85±23.39	32.60±21.84	**0.20**[a]

Values are mean±standard deviation.
[a] Wilcoxon signed rank test.
[b] Paired t-test.
[*] p<0.05 between groups.

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Table 4 – The scores in numerical rating scale (NRS), 5-D pruritus scale, Leuven Itch Scale after third ESWT sessions.

	ESWT After 3 therapy	Control After 3 therapy	p
NRS	3. 57±2.09	5.35±2.31	0.009[a]
5-D pruritus scale			
Duration	1.39±0.66	1.65±1.07	0.49[b]
Degree	2.52±0.59	2.96±0.93	0.15[b]
Direction	2.78±0.90	3.48±1.08	0.033[b]
Disability	2.35±1.23	2.87±1.18	0.17[b]
Leuven Itch Scale			
Frequency	67.39±23.15	72.83±19.81	0.42[b]
Duration	20.09±25.83	43.04±37.80	0.033[b]
Severity	35.22±20.20	53.48±23.08	0.007[a]
Consequences	17.19±16.24	32.60±21.84	0.009[a]

Values are mean±standard deviation.
[a] Independent t-test.
[b] Mann-Whitney test.

4. Discussion

This study's results indicate that ESWT significantly reduced burn scar pruritus severity and activities-of-daily-living disturbances in the experimental group. We objectively assessed perfusion levels of the burn area after ESWT and noted an increase in perfusion. This suggests that the intensity of ESWT used in this study is useful for pruritus in burn scars. It is important to point out that no study has clarified the optimal time, frequency, and dose of ESWT.

The phases of wound healing in response to trauma (including burn injuries) are the inflammatory, proliferative, and remodeling phases. The term "acute" pruritus refers to the period from wound closure to approximately 6 months, whereas the term "chronic" pruritus applies to a period for up to 2 years after injury [10]. Pruritus has two causes, a peripheral and central cause. The primary mediator of pruritus is a histamine. In addition to the histamine, there are several inflammatory mediators, such as SP, a platelet activating factor, etc. The stimulus from histamine receptors is transmitted via activated unmyelinated C nerve fibers. Another study showed low nerve fiber density in burn scars; however, there was an increase in the number of SP-positive nerve fibers. At the level of the wound, SP has been found to sensitize mast cells and enhance the release of inflammatory materials. Calcitonin gene-related peptide (CGRP) is another neuropeptide, whose function is vasodilation and the potentiation of effects caused by SP. SP and CGRP mediate neurogenic inflammation and mediate nociceptive processing [11–14]. Pruritusis thought to be a similar form of pain according to several studies. Pruritus and pain share C fiber nerve endings, a group of dorsal horn interneurons in the spinal cord, and a tract in anterolateral spinothalamic tract fibers. Although pruritus and pain share common pathways, their underlying mechanisms may be distinct [15].

ESWT is commonly used to treat many musculoskeletal diseases. Many studies have investigated the mechanisms that result in a mechanosensitive feedback between the acoustic impulse and stimulated cells. These concepts explain the potential role of ESWT in regenerative therapy. Extracorporeal shock wave energy can cause alterations to the target cells. These interactions involve intra-cell and cell-matrix interactions. The production of proteins, nitric oxide, and specific growth factors contributes to the activation of the biological process [4]. Several studies have proposed that ESWT may have effects in orthopedics (bone union and tendinopathy) and dermatology (wound healing). It is reasonable to believe that ESWT may induce a biologic effect, with mitogenic, osteogenic, and angiogenic responses [16,17]. ESWT is considered a method of mechanotherapy, and it achieves tissue regeneration by inhibiting inflammation [18,19]. Several studies have also reported that ESWT was effective in treating chronic pain by the selective loss of unmyelinated nerve fibers [20] and hyperstimulation analgesia [21]. Neuropeptides cause so-called "neurogenic inflammation," which is an inflammation that results from the release of substances (e.g., SP and CGRP) from primary sensory nerve endings. Nerve fiber loss and the depletion of neuropeptides might decrease inflammation and chronic pain [22,23]. Moreover, recent reports have demonstrated that flap tissue perfusion significantly increased via increasing vascular endothelial growth factor expression under the optimal dosage of ESWT [24]. The LDI is a standard evaluation tool for determining perfusion and microcirculation correlated with tissue ischemia. Perfusion is directly correlated with arteriogenesis [25]. ESWT may lead to an increase of perfusion and thus to a better blood supply as well as to the prevention of ischemia, a major problem in the zone of stasis caused by an acute burn wound and heat stimulation [26]. Even treating a remote skin area with ESWT is beneficial for enhancing blood flow and angiogenesis [27]. Yosipovitch et el. [13] reported that noxious heat (49°C), pain, and scratching increase resting skin blood flow, and these stimulations have a significant inhibitory effect on histamine-induced hyperemia simultaneously that they reduce itch intensity. No correlations were noted between the reduction of histamine-induced skin perfusion and pruritus intensity. They reported the difference of reactions to stimuli between resting skin perfusion and histamine-induced skin perfusion, and these counter stimuli operated by masking the subjective pruritus and hence could inhibit hyperemic skin blood flow. But our study showed that ESWT was effective for reducing burn scar pruritus and resulted in an immediate increase of capillary perfusion. This result supports that other neurogenic mechanisms unrelated to an effect on skin perfusion can attenuate pruritus.

Several studies have described the use of ESWT in burn injuries. Fioramonti et al. suggested that the action of ESWT is to mechanically disrupt the tissue by cavitation and cause tissue repair through a neovascularization mechanism [28]. Ottoman et el. reported that the regeneration mechanisms of ESWT on burn wounds were increased vascularization, anti-inflammatory action, enhanced secretions of growth factors, and fibroblast recruitment [26,29,30]. They explained that the

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histological findings were important for improvement in the healing of the burn wound after ESWT [27]. Additionally, another study reported the 6-month follow-up revealed a healed wound without scarring [31].

Neurogenic inflammation plays an important role in the pathogenesis of burn scar pruritus. The reduction of neuropeptides has a crucial role in ESWT-mediated effects in the treatment of pruritus. Further studies regarding the treatment intensity, frequency, and interval of ESWT are necessary since only treatment for neuropathic pain was examined in the present study. In addition, ESWT was performed in patients who had achieved re-epithelialization and were admitted to the Department of Rehabilitation Medicine; therefore, the effects of ESWT for the management of acute pruritus during the inflammation and chronic remodeling phases of burn wound healing were not examined in our study. Therefore future investigations are indicated to determine the responses at different time points.

5. Conclusions

This is the first report of the use of ESWT in burn patients with burn scar pruritus. We found that ESWT is clinically useful as a non-invasive therapy for pruritus, and it should be considered an effective alternative modality for the treatment of burn scar pruritus.

Conflict of interest

The authors declare no potential conflict of interest.

Acknowledgments

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