

Extracorporeal Shockwave Therapy in Patients with Morton's Neuroma

A Randomized, Placebo-Controlled Trial

Hyun Seok, MD, PhD*
Sang-Hyun Kim, MD, PhD*
Seung Yeol Lee, MD*
Sung Won Park, MD*

Background: The aim of this study was to evaluate the efficacy of extracorporeal shockwave therapy (ESWT) for the treatment of Morton's neuroma by measuring changes in patient pain, function, and neuroma size.

Methods: Patients with Morton's neuroma were randomly assigned to either the ESWT group or the sham stimulation group. Outcome measures, including visual analog scale (VAS) and American Orthopaedic Foot and Ankle Society lesser toes (AOFAS) scores, were assessed at baseline and 1 and 4 weeks after treatment. The Johnson satisfaction test was also performed 1 and 4 weeks after treatment. The neuroma diameter was measured using ultrasonography at baseline and 4 weeks after treatment.

Results: Patients receiving ESWT exhibited significantly decreased VAS scores 1 and 4 weeks after treatment relative to baseline, and AOFAS scores were significantly improved 4 weeks after treatment relative to baseline. In the sham stimulation group, VAS and AOFAS scores showed no significant changes at any time after treatment. Neither group showed significant changes in Johnson satisfaction test results or neuroma diameter.

Conclusions: These results suggest that ESWT may reduce pain in patients with Morton's neuroma. (J Am Podiatr Med Assoc 106(2): 93-99, 2016)

Morton's neuroma is a common cause of foot pain, which worsens with walking. It is characterized by thickening of the common plantar digital nerve at the bifurcation, secondary to compression by the overlying transverse metatarsal ligament, which can induce nerve fiber degeneration, endoneural edema, and perineural fibrous tissue formation, resulting in an enlarged nerve.¹⁻³

Diagnosis of Morton's neuroma is based primarily on patient history and clinical examination. There is a tender point at the intermetatarsal space with altered sensation, and a palpable click with compression.⁴ Diagnostic methods such as ultrasonography and magnetic resonance imaging are generally performed to confirm the diagnosis.⁵ Manage-

ment of Morton's neuroma is usually conservative and includes footwear modification, orthoses, and nonsteroidal anti-inflammatory medications. Corticosteroid injections, nerve block with alcohol, and surgical neurectomy can be effective, but these invasive methods can also induce several adverse effects.⁶⁻⁸

Extracorporeal shock waves are sonic pulses of microsecond duration that can be focused on a target site. It has been suggested that extracorporeal shock waves can suppress inflammatory responses and inhibit pain receptors.⁹⁻¹¹ Several animal studies have demonstrated that extracorporeal shockwave therapy (ESWT) suppresses nociceptive nerve fibers, which may also reduce pain in focal neuropathic disease.¹²⁻¹⁴ Although the precise mechanism of ESWT has not been established, the authors hypothesized that the effects of ESWT may reduce the pain and disability associated with Morton's neuroma. Thus, the aim of this study was to evaluate the effectiveness of ESWT in the

*Department of Rehabilitation Medicine, Soonchunhyang University College of Medicine, Bucheon, Republic of Korea.

Corresponding author: Sang-Hyun Kim, Department of Rehabilitation Medicine, Soonchunhyang University College of Medicine, Bucheon, 1174 Jung-dong, Bucheon-si, Gyeonggi-do 420767, Republic of Korea. (E-mail: sanghyunkim71@gmail.com)

management of Morton's neuroma multilaterally by measuring changes in pain, functional scale scores, patient satisfaction, and neuroma size after ESWT application.

Patients and Methods

All of the participants were informed of the procedures and objectives of the study, as well as possible complications. Only patients who provided informed consent were included. Ethical approval was obtained from the Institutional Human Research Ethics Committee of Soonchunhyang University College of Medicine (Bucheon, Gyeonggi-do, Republic of Korea).

Participants

This randomized, placebo-controlled trial was conducted on patients with Morton's neuroma referred to the rehabilitation clinic of Soonchunhyang University Hospital, Bucheon. All of the participants were at least 19 years old, had symptoms for at least 3 months that were aggravated by walking, and tested positive for Mulder's sign. The diagnosis was confirmed by ultrasonography. The exclusion criteria were as follows: pregnancy; having more than one Morton's neuroma; having other foot pathologic disorders, including tendinopathy, bursitis, arthritis, vasculitis, and infectious diseases; having other neurologic abnormalities; receiving anticoagulant therapy; having received treatment in the affected area within the previous 6 months; and having received ESWT to any other body lesion. The participants were instructed to refrain from using any other treatment, including physical modalities, pain medications, corticosteroid injections, and foot orthoses, during their participation in this study.

Study Procedures

Each patient was assigned the next sequentially ordered study pack, which contained all of the study questionnaires and a sealed, opaque envelope containing a note pertaining to randomization. Patients were block randomized (blocks of four) to either the ESWT group or the sham stimulation group by an independent physician using a computerized random number generator. Before the intervention, the point of ESWT or sham stimulation was marked by the physician who performed the ultrasonography. Participants in the ESWT group received one session of ESWT consisting of 1,000 shocks at 3 Hz per lesion (PiezoWave; Richard Wolf

GmbH, Knittlingen, Germany). The probe was oriented perpendicular to the patient's sole, and ultrasound gel was used as a coupling agent (Fig. 1A). The energy level was set to the maximum level tolerated by the patient (0.12–0.24 mJ/mm²).

Participants in the sham stimulation group received one session of sham ESWT intervention. To enhance the sham design, the machine made a noise with every shock wave delivered at a minimal energy level (0.03 mJ/mm²), and while the probe contacted the lesion of interest, the pulse orientation was parallel to the patient's sole (Fig. 1B). All of the participants were blindfolded during the ESWT, which was applied by a physician (S.W.P.) with 4 years of experience who was blinded to the study procedures.

Ultrasonographic Evaluation

All of the ultrasonography scans were performed by a musculoskeletal ultrasonographic physician (S.Y.L.) with 5 years of experience who was blinded to the other study procedures. Ultrasonography was performed with the patient in the supine position with the ankle in the neutral position using 9- to 12-MHz linear array transducers (SSA-660A; Toshiba, Tokyo, Japan). Ultrasonographic images were obtained from the sole of the foot, and the diameter of Morton's neuroma was measured as the largest transverse diameter (long axis) in the coronal plane (Fig. 2). Ultrasonography was conducted before treatment and 4 weeks after treatment.

Outcome Measures

Participants were assessed before ESWT or sham treatment by a single physician who was blinded to the other study procedures. Parameters were assessed by a 100-mm visual analog scale (VAS) for forefoot pain and by the American Orthopaedic Foot and Ankle Society lesser toes (AOFAS) score. Postintervention evaluations, including the Johnson satisfaction test, were performed 1 and 4 weeks after the intervention by the same investigator.

Statistical Analysis

All of the data were analyzed using a statistical software program (SPSS for Windows, version 15.0; SPSS Inc, Chicago, Illinois). The Mann-Whitney *U* test (for continuous data) and the χ^2 test (for categorical data) were used to compare the demographic characteristics and baseline parameters of participants. The Friedman test was used to

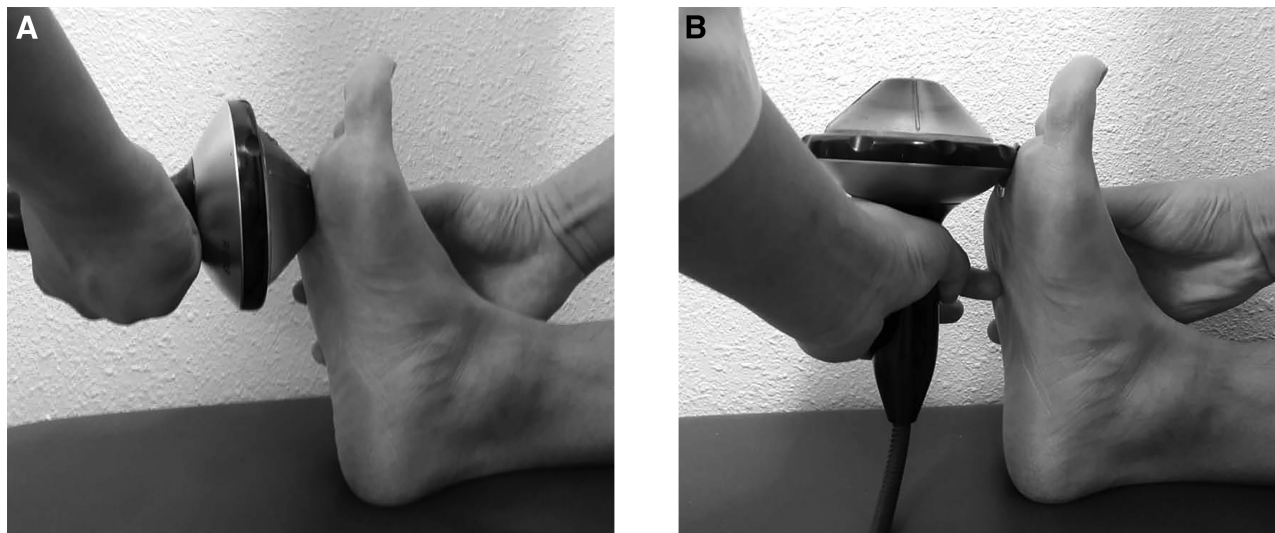


Figure 1. Probe placement during extracorporeal shockwave therapy (A) and sham stimulation (B).

compare outcome measures within each group; if the Friedman statistic was significant, the Wilcoxon signed rank test was used to compare outcomes at each follow-up session with baseline values. Differences between groups were investigated using the Mann-Whitney *U* test. A $P < .05$ was considered statistically significant.

Results

Of the 30 eligible patients, 15 were allocated to the ESWT group and 15 to the sham stimulation group. However, four patients dropped out: two did not

participate in the follow-up session (one in the ESWT group and one in the sham group) and two received another type of treatment during follow-up (both in the sham group). In total, 26 participants completed this randomized controlled trial. The most common lesion site in both groups was the third web space. There were no statistically significant differences in age, sex, duration of symptoms, or initial clinical outcomes between the two groups (Table 1).

Figure 3 shows the mean $\pm$ SD values of clinical outcomes in both groups. The mean $\pm$ SD VAS score in the ESWT group showed significant

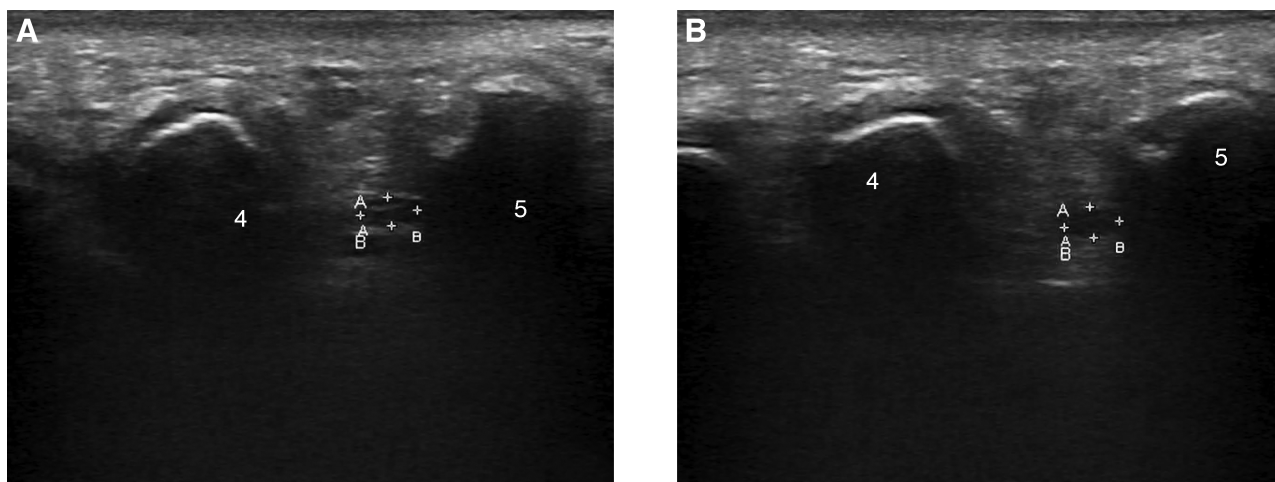


Figure 2. Ultrasonography of the second intermetatarsal space in the coronal plane revealed an ovoid, hypoechoic nodule. A, In the long axis of the baseline image, the diameter of the neuroma was 3.5 mm. B, Four weeks after a single session of extracorporeal shockwave therapy (energy level, 0.24 mJ/mm²), the diameter of the neuroma was 3.4 mm.

Table 1. Baseline Characteristics of the Participants in Each Group

Characteristic	ESWT Group (n = 14)	Sham Group (n = 12)	P Value
Sex (M/F [No.])	5/9	4/8	.899
Age (mean $\pm$ SD [years])	58.5 $\pm$ 13.4	54.5 $\pm$ 14.3	.221
Duration of symptoms (mean $\pm$ SD [mo])	6.8 $\pm$ 3.3	7.2 $\pm$ 3.4	.257
Site of neuroma (No.)			
First web space	2	1	>.99
Second web space	4	4	>.99
Third web space	6	5	.951
Fourth web space	2	2	>.99
Baseline VAS score (mean $\pm$ SD)	64.2 $\pm$ 18.6	48.1 (16.2)	.07
Baseline AOFAS score (mean $\pm$ SD)	67.6 $\pm$ 18.9	74.7 (13.4)	.475

Abbreviations: AOFAS, American Orthopaedic Foot and Ankle Society lesser toes; ESWT, extracorporeal shockwave therapy; VAS, visual analog scale.

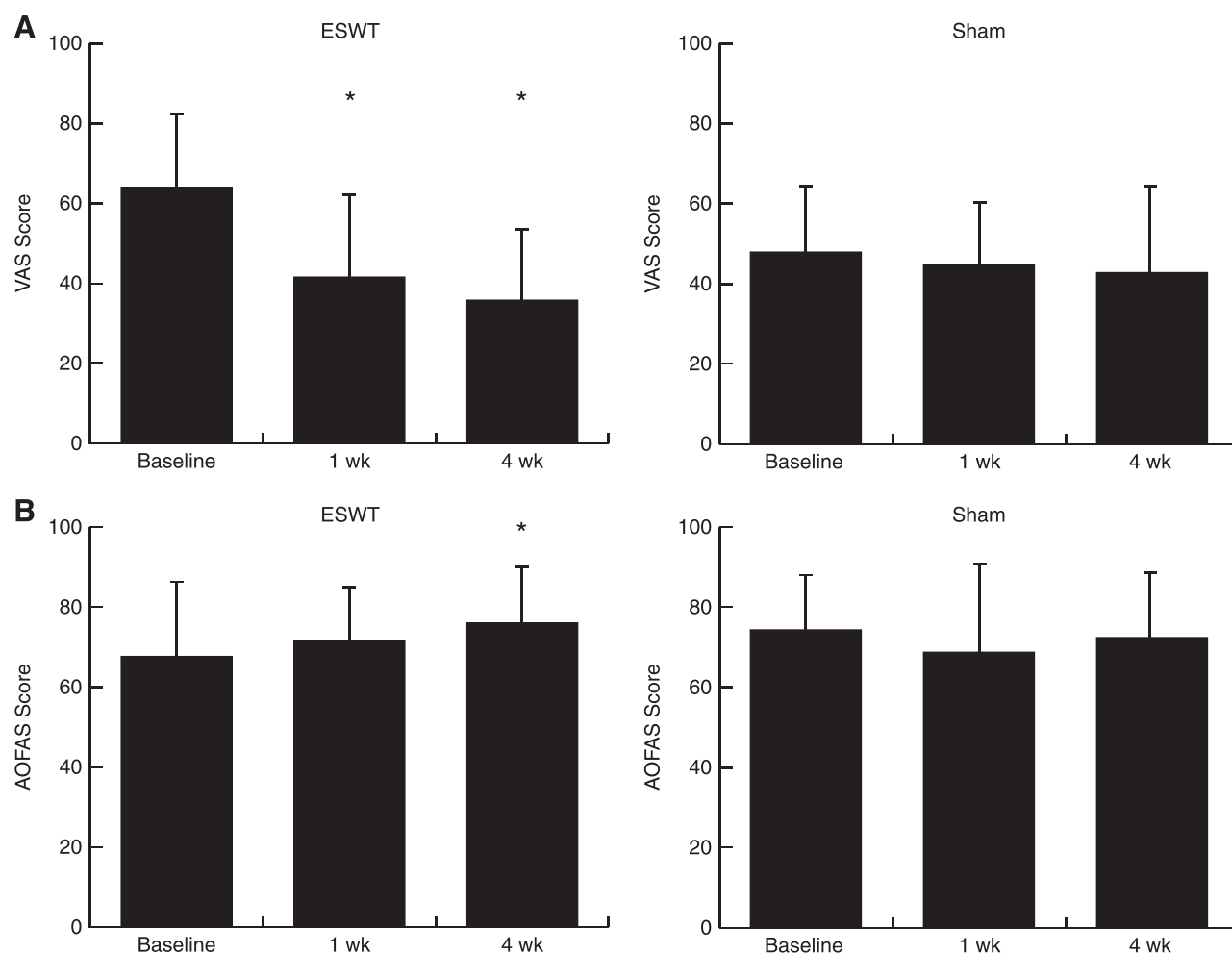


Figure 3. Mean $\pm$ SD visual analog scale (VAS) (A) and American Orthopaedic Foot and Ankle Society lesser toes (AOFAS) (B) scores in the extracorporeal shockwave therapy (ESWT) and sham stimulation groups. * P < .05 versus baseline.

improvement 1 week (41.6 ± 20.6) and 4 weeks (35.9 ± 17.8) after treatment compared with baseline ($P < .05$). However, the sham stimulation group showed no significant change. There was no significant difference in VAS score between the ESWT and sham groups during the study.

The mean $\pm$ SD AOFAS score in the ESWT group showed significant improvement 4 weeks after treatment (76.3 ± 14.1) compared with baseline ($P < .05$) (Fig. 3B). The sham group showed no significant change. There was no significant difference in AOFAS score between the ESWT and sham groups during the study. The Johnson satisfaction test result showed no significant difference between the ESWT and sham groups during the study (Fig. 4).

According to baseline ultrasonography, the longest mean $\pm$ SD neuroma diameter was 3.96 ± 0.46 mm in the ESWT group and 4.10 ± 0.63 mm in the sham group. Four weeks after treatment, the mean $\pm$ SD diameter of Morton's neuroma was slightly reduced in both groups (3.73 ± 0.75 mm in the ESWT group and 3.89 ± 0.58 mm in the sham group), but the difference was not statistically significant. No patients reported adverse effects during the study.

Discussion

This trial revealed that a single ESWT treatment of Morton's neuroma significantly improved VAS and AOFAS scores up to 4 weeks after treatment. Although the exact mechanism of ESWT has not

been confirmed, one possible mechanism for the pain reduction induced by ESWT is the suppression of nociceptive neuropeptides. Substance P and calcitonin gene-related peptide (CGRP), which are abundant in neuroma tissues such as Morton's neuroma, are involved in nociceptive transmission and neurogenic inflammation.¹⁵⁻¹⁸ Several reports using animal models have suggested that ESWT can reduce CGRP and substance P levels in the nervous system. For example, Ohtori et al¹² reported the loss of immunoreactivity for CGRP after ESWT application. Hausdorf et al¹³ found that immunoreactivity for substance P was reduced after applying ESWT on the hind limb in rabbits. Thus, we hypothesized that ESWT may reduce the pain of Morton's neuroma by suppressing substance P and CGRP levels. Further studies including the evaluation of immunoreactivity in Morton's neuroma specimens after ESWT are needed to confirm this.

The diameter of Morton's neuroma did not decrease significantly after applying ESWT despite the pain reduction observed in these results. In contrast, alcohol injection into Morton's neuroma can reduce the diameter of the neuroma by up to 30%.¹⁹ Alcohol injection induces chemical neurolysis, especially in large myelinated nerve fibers, resulting in a reduction in size of Morton's neuroma.²⁰ In comparison, ESWT may selectively affect substance P and CGRP immunoreactive nerve fibers, mostly unmyelinated (diameters, $0.52 \mu\text{m}$) or lightly myelinated ($2\text{--}6 \mu\text{m}$) nerve fibers, with smaller diameters than the large myelinated nerve

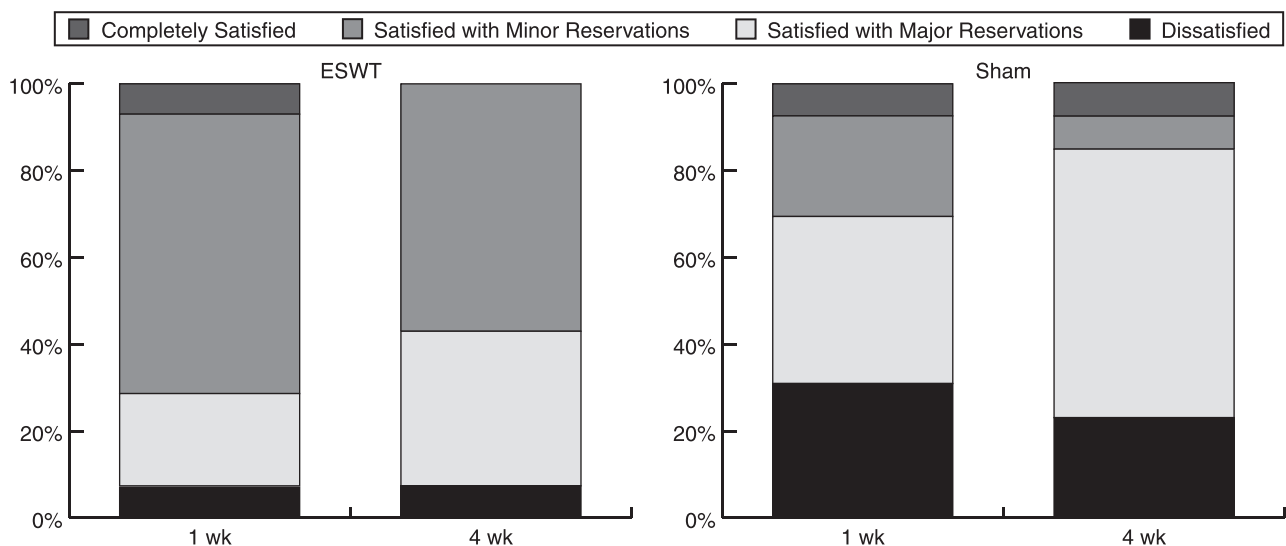


Figure 4. Results of the Johnson satisfaction test show no significant changes at any posttreatment time point in either group. ESWT, extracorporeal shockwave therapy.

fibers (6–12 μm).¹⁴ Thus, ESWT would be expected to have a limited effect on size reduction of Morton's neuroma, consistent with the present results.

According to Johnson satisfaction test results, ESWT did not satisfy the patients significantly. In the ESWT group, the overall rate of patients who responded “completely satisfied” or “satisfied with minor reservations” at 4 weeks was 57%, which is lower than reported patient satisfaction with other treatments. In a study of the effects of corticosteroid injection on Morton's neuroma, the overall rate of patients who were “completely satisfied” at 6 weeks was 84%.²¹ Moreover, one study on alcohol neurolysis for Morton's neuroma showed that 62% of patients were “completely satisfied” after multiple alcohol injections.¹⁹ These outcomes may indicate that the degree of pain reduction after ESWT was small compared with that after corticosteroid injections or alcohol neurolysis, resulting in a lower satisfaction level. However, corticosteroid injections and alcohol neurolysis are relatively invasive treatments, which may not be useful in patients with a tendency to bleed, and they can induce various adverse effects, such as skin thinning, fat atrophy, hyperpigmentation, and complex regional pain syndrome.^{6,7,19}

Note that this study was limited by its small sample size and lack of long-term follow-up. However, this study strictly excluded any other treatments, such as medications or orthotic devices. Longer follow-up was not possible due to ethical considerations, especially in the sham stimulation group. However, AOFAS scores showed significant improvement 4 weeks after ESWT treatment (but not 1 week after ESWT), and VAS scores showed improvement at 4 weeks compared with 1 week after ESWT (not significant); therefore, the effectiveness of ESWT may be prolonged over 4 weeks.

Conclusions

In patients with Morton's neuroma, ESWT may have potential as a therapeutic option for decreasing pain and improving function. Further investigations into the application of ESWT in Morton's neuroma are needed to confirm the findings of this study and to establish the mechanism of ESWT.

Financial Disclosure: This research was supported by the Soonchunhyang University Research Fund.

Conflict of Interest: None reported.

References

1. HASSOUNA H, SINGH D: Morton's metatarsalgia: pathogenesis, aetiology and current management. *Acta Orthop Belg* **71**: 646, 2005.
2. WU KK: Morton's interdigital neuroma: a clinical review of its etiology, treatment, and results. *J Foot Ankle Surg* **35**: 112, 1996.
3. MORSCHER E, ULRICH J, DICK W: Morton's intermetatarsal neuroma: morphology and histological substrate. *Foot Ankle Int* **21**: 558, 2000.
4. MULDER JD: The causative mechanism in morton's metatarsalgia. *J Bone Joint Surg Br* **33**: 94, 1951.
5. LEE MJ, KIM S, HUH YM, ET AL: Morton neuroma: evaluated with ultrasonography and MR imaging. *Korean J Radiol* **8**: 148, 2007.
6. DOCKERY GL: The treatment of intermetatarsal neuromas with 4% alcohol sclerosing injections. *J Foot Ankle Surg* **38**: 403, 1999.
7. REDDY PD, ZELICOF SB, RUOTOLO C, ET AL: Interdigital neuroma: local cutaneous changes after corticosteroid injection. *Clin Orthop Relat Res* **317**: 185, 1995.
8. LEE KT, KIM JB, YOUNG KW, ET AL: Long-term results of neurectomy in the treatment of Morton's neuroma: more than 10 years' follow-up. *Foot Ankle Spec* **4**: 349, 2011.
9. HAUPT G, CHVAPIL M: Effect of shock waves on the healing of partial-thickness wounds in piglets. *J Surg Res* **49**: 45, 1990.
10. MARIOTTO S, DE PRATI AC, CAVALIERI E, ET AL: Extracorporeal shock wave therapy in inflammatory diseases: molecular mechanism that triggers anti-inflammatory action. *Curr Med Chem* **16**: 2366, 2009.
11. CIAMPA AR, DE PRATI AC, AMELIO E, ET AL: Nitric oxide mediates anti-inflammatory action of extracorporeal shock waves. *FEBS Lett* **579**: 6839, 2005.
12. OHTORI S, INOUE G, MANNOJI C, ET AL: Shock wave application to rat skin induces degeneration and reinnervation of sensory nerve fibres. *Neurosci Lett* **315**: 57, 2001.
13. HAUSDORF J, LEMMENS MA, KAPLAN S, ET AL: Extracorporeal shockwave application to the distal femur of rabbits diminishes the number of neurons immunoreactive for substance P in dorsal root ganglia L5. *Brain Res* **1207**: 96, 2008.
14. HAUSDORF J, LEMMENS MA, HECK KD, ET AL: Selective loss of unmyelinated nerve fibers after extracorporeal shock-wave application to the musculoskeletal system. *Neuroscience* **155**: 138, 2008.
15. GALEAZZA MT, GARRY MG, YOST HJ, ET AL: Plasticity in the synthesis and storage of substance P and calcitonin gene-related peptide in primary afferent neurons during peripheral inflammation. *Neuroscience* **66**: 443, 1995.
16. ZOCHODNE DW, THERIAULT M, SHARKEY KA, ET AL: Peptides and neuromas: calcitonin gene-related peptide, substance P, and mast cells in a mechanosensitive human sural neuroma. *Muscle Nerve* **20**: 875, 1997.
17. LINDQVIST A, RIVERO-MELIAN C, TURAN I, ET AL: Neuropep-

- tyrosine hydroxylase-immunoreactive nerve fibers in painful Morton's neuromas. *Muscle Nerve* **23**: 1214, 2000.
18. HOLZER P: Local effector functions of capsaicin-sensitive sensory nerve endings: involvement of tachykinins, calcitonin gene-related peptide and other neuropeptides. *Neuroscience* **24**: 739, 1988.
 19. HUGHES RJ, ALI K, JONES H, ET AL: Treatment of Morton's neuroma with alcohol injection under sonographic guidance: follow-up of 101 cases. *AJR Am J Roentgenol* **188**: 1535, 2007.
 20. RENGACHARY SS, WATANABE IS, SINGER P, ET AL: Effect of glycerol on peripheral nerve: an experimental study. *Neurosurgery* **13**: 681, 1983.
 21. MAKKI D, HADDAD BZ, MAHMOOD Z, ET AL: Efficacy of corticosteroid injection versus size of plantar interdigital neuroma. *Foot Ankle Int* **33**: 722, 2012.