

# Extracorporeal Shockwave Treatment for Chronic Diabetic Foot Ulcers



**Background and Purpose:** Diabetic foot ulcer is caused by ischemia/hypoxia due to occlusion of small vessel associated with neuropathy and secondary infection. Extracorporeal shockwave treatment (ESWT) was shown to induce the ingrowth of neovascularization associated with increased angiogenic growth factors such as eNOS, VEGF and PCNA. Recent studies reported the effectiveness of ESWT in acute and chronic wounds. Others demonstrated the antibacterial effect of ESWT in experimental studies. It is reasonable to speculate that ESWT may be effective in chronic diabetic foot ulcers. The purpose of this prospective study was to evaluate the efficacy of ESWT in chronic diabetic foot ulcers and to compare the results with that of hyperbaric oxygen therapy (HBO), and to investigate the regeneration effects after treatment.

**Methods:** Seventy patients with 72 chronic diabetic foot ulcers were randomly divided into two groups. The ESWT group consisted of 34 patients with 36 ulcers and 36 patients with 36 ulcers in the HBO group. Both groups showed similar demographic characteristics. Patients in ESWT group received 300 + 100/cm<sup>2</sup> of treatment area impulses of shockwave at 0.11 mJ/cm<sup>2</sup> energy flux density once every two weeks for 6 weeks. Patients in HBO group received HBO therapy in a sealed chamber at the pressure of 2.5 ATA once a day, 5 days a week for a total of 20 treatments. Local blood flow perfusion, bacterial culture, and biopsy were performed before and after treatment. The evaluations included clinical assessment on the healing status of the ulcer with photo-documentation, blood flow perfusion scan, bacteriological study, histomorphological examination and immunohistochemical analysis.

**Results:** The overall results showed completely healed in 31%, improved in 58% and unchanged in 11% for the ESWT group; and 22% completely healed, 50% improved and 28% unchanged for HBO group in favor of ESWT group (P = 0.001). ESWT group showed significantly better local blood flow perfusion rate (Table 1, Fig. 1-a and Fig. 1-b) and considerably higher cell concentration and more active proliferation and than HBO (Fig. 2-a and Fig. 2-b). The results of bacteria culture revealed significant decreases in the bacteria colony counts after treatment (Table 2). On immunohistochemical analysis, ESWT group showed significant increases in eNOS, VEGF and PCNA expressions and a decrease in TUNEL expression than the HBO group (Table 3, Fig. 3-a-1, 3-a-2, Fig. 3-b-1, 3-b-2, Fig. 3-c-1, 3-c-2, Fig. 3-d-1 and 3-d-2).

**Discussion:** The causes of diabetic foot ulcer are multi-factorial including ischemia/hypoxia, neuropathy, and infection, and they often coexist. Management of chronic diabetic skin ulcers requires multidisciplinary approach including the control of diabetes, antibiotic, shoe wear, wound care and surgery in selected cases. The results of the customary standard treatments are inconsistent and most are less satisfactory. Therefore, many adjunctive therapies are designed with the intention to cure the diabetic foot ulcers including hyperbaric oxygen therapy, ultrasound, recombinant platelet-derived growth factor-BB, vacuum assisted wound closure and acellular matrix. Among them, HBO is the most commonly employed modality at our institution. Some studies showed beneficial effects, however, none showed universal success. The results of the current study showed that ESWT is more effective than HBO in chronic diabetic foot ulcers.

The exact mechanism of ESWT remains unclear. The results of this study demonstrated that clinical improvement of the ulcers after ESWT were associated with increases in angiogenesis and improvement in local blood flow perfusion, and decreases in cell apoptosis and bacteria growth.

**Conclusions:** ESWT is more effective than HBO in the treatment of chronic diabetic foot ulcers. It appears that application of ESWT appears to result in tissue regeneration in chronic diabetic foot ulcers.

**This information is being provided for educational purposes only. The dermaPACE® is limited by federal law to investigational use. It is not for sale in the US.**

Table 1 Blood Flow Perfusion Rate Before and After Treatment

Laser Doppler	Before treatment	After treatment	P-value-1
ESWT			
Mean±SD	0.64±0.28	0.75±0.19	0.04
(Range)	(0.19-1.23)	(0.46-1.28)	
HBO			
Mean±SD	0.50±0.21	0.58±0.11	0.140
(Range)	(0.18-0.6)	(0.51-0.66)	
P-value-2	0.30		0.043

P-value-1: Comparison of data before and after treatment in the same group.

P-value-2: Comparison of data between ESWT and HBO

Table 2 The Results of Bacteriological Examination

Bacteria growth*	0	I	II	III	VI	P-value-1
ESWT group						
Before treatment	4	3	9	17	3	
After treatment	13	4	11	8	0	0.002
HBO group						
Before treatment	5	3	9	15	4	
After treatment	11	0	12	12	1	0.042
P-value-2						0.984
P-value-3						0.198

P-value-1: Comparison of data before and after treatment within the same group

P-value-2: Comparison of data between the two groups before treatment

P-value-3: Comparison of data between the two groups after treatment

\*0: No growth; I: Rare growth; II: Light growth; III: Moderate growth; VI: Heavy growth

Table 3 The Results of Immunohistochemical Analysis.

Mean±SD (Range)	Before treatment	After treatment	P-value-1
eNOS			
ESWT	26.62±14.87 (4-57)	48.67±18.82 (6-72)	<0.001
HBO	25.2±17.09 (6-53)	20.08±9.73 (6-30)	0.317
P-value-2	0.438	<0.001	
VEGF			
ESWT	31.36±22.27 (8-90)	63.69±21.06 (25-91)	<0.001
HBO	42.6±12.6 (28-55)	44.40±11.24 (30-56)	0.409
P-value-2	0.086	0.042	
PCNA			
ESWT	27.0±15.15 (7-53)	55.9±27.86 (8-95)	0.005
HBO	23.0±2.83 (20-26)	26.20±3.11 (23-30)	0.064
P-value-2	0.188	0.004	
TUNEL			
ESWT	62.42±15.0 (39-82)	31.58±13.44 (14-56)	<0.001
HBO	64.0±25.58 (23-86)	49.4±17.0 (22-65)	0.162
P-value-2	0.451	0.04	

eNOS: Endothelial nitric oxide synthase; VEGF: Vessel endothelial growth factor; PCNA: proliferation cell nuclear antigen; TUNEL: Transference-mediated digoxigenin-deoxy-UTP nick end labeling

P-value-1: Comparison of data before and after treatment within the same group.

P-value-2: Comparison of data between ESWT and HBO.

Fig. 1. Laser Doppler scan showed significant increases in blood flow perfusion rate after ESWT (Fig. 1-a), whereas the changes were not significant after HBO (Fig. 1-b).

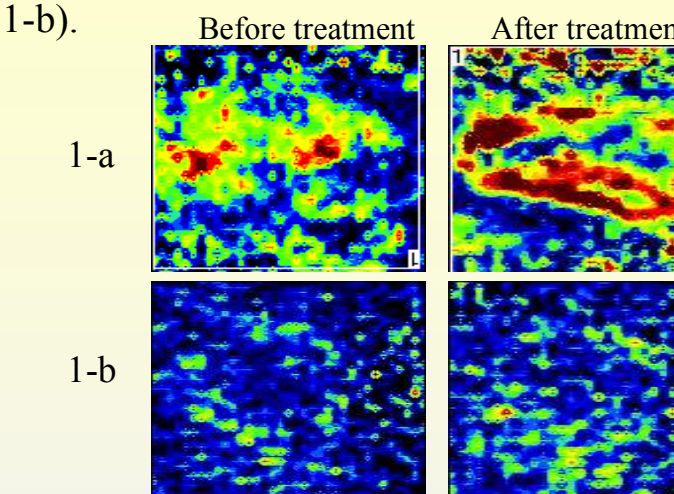


Fig. 3a. Microscopic features of immunohistochemical stain showed significant increases in eNOS expression after ESWT (Fig. 3-a-1), whereas the changes were not significant after HBO (Fig. 3-a-2).

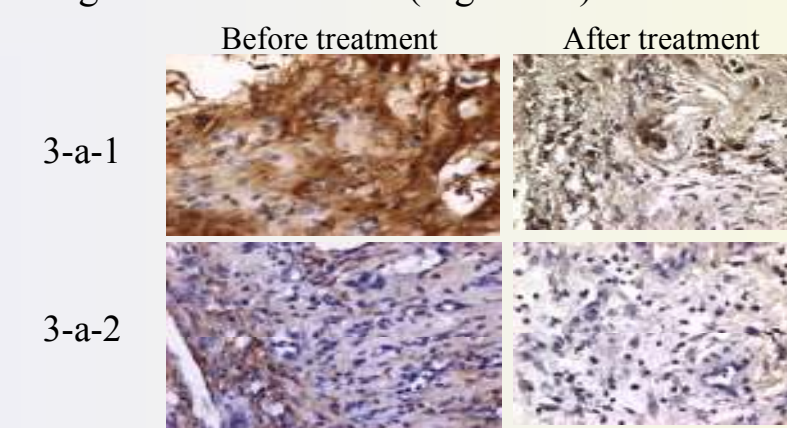


Fig. 3c. Microscopic features of immunohistochemical stain showed significant increases in PCNA expression after ESWT (Fig. 3-c-1), whereas the changes were not significant after HBO (Fig. 3-c-2).

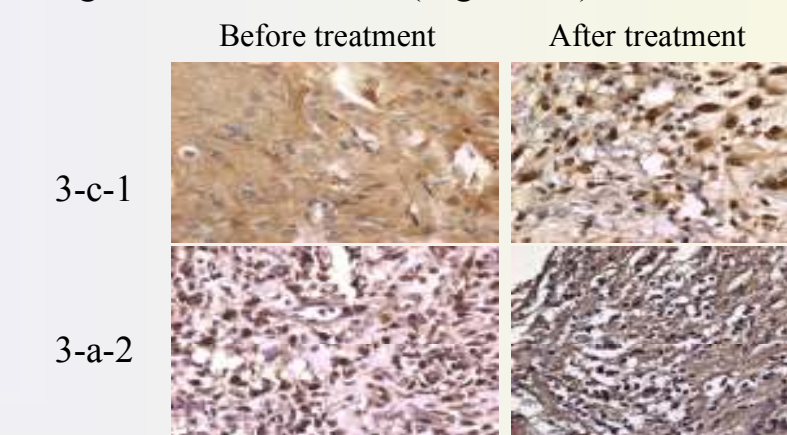


Fig. 2. Microscopic features of the biopsy specimen showed higher cell concentration and more active cell proliferation after ESWT (Fig. 2-a), and less cell concentration and proliferation after HBO (Fig. 2-b) (H-E stain x 40).

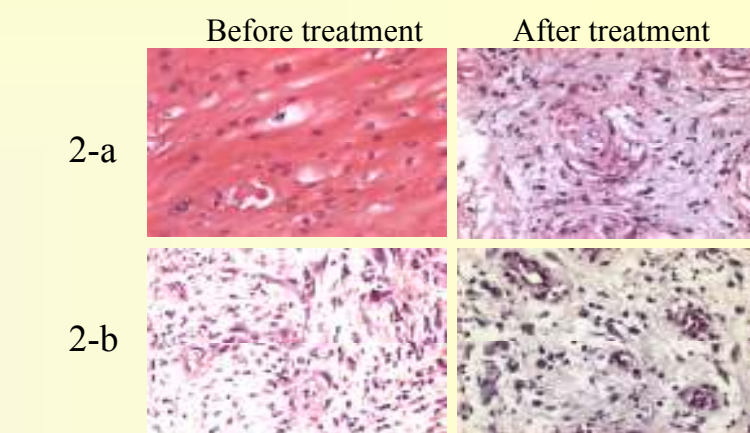


Fig. 3b. Microscopic features of immunohistochemical stain showed significant increases in VEGF expression after ESWT (Fig. 3-b-1), whereas the changes were not significant after HBO (Fig. 3-b-2).

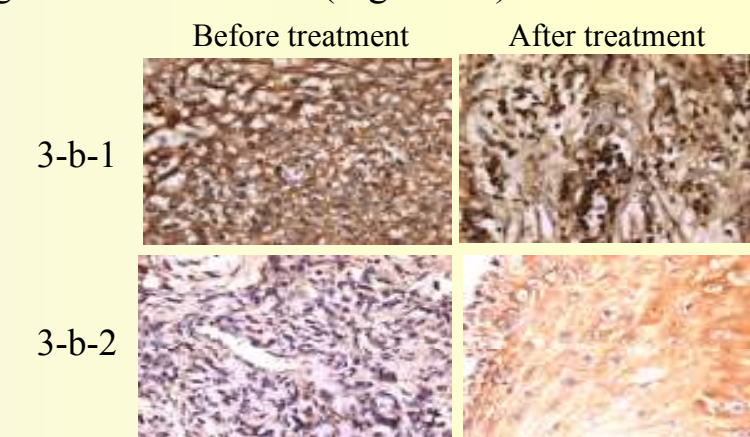
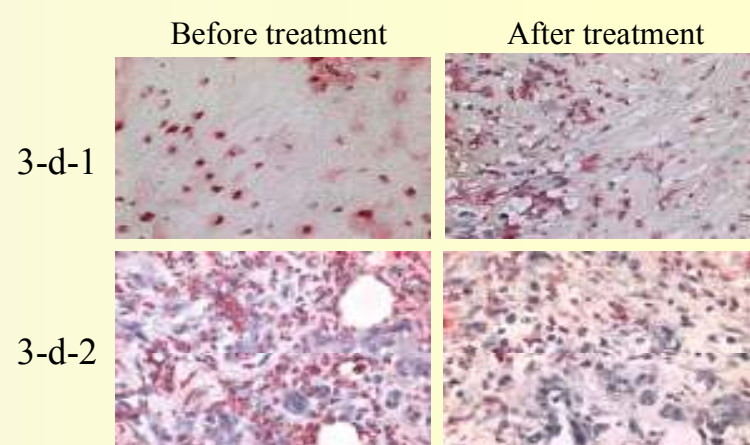


Fig. 3d. Microscopic features of immunohistochemical stain revealed significant decreases in TUNEL expression after ESWT (Fig. 3-d-1), whereas the changes were not significant after HBO (Fig. 3-d-2).



## References:

- Bigido SA, Boc SF, Lopez RC. Effective management of major lower extremity wounds using an acellular regenerative tissue matrix: a pilot study. *Orthopedics* 2004;27(1):s145-9.
- Ennis WJ, Foreman P, Mozen N, Massey J, Conner-Kerr T, Meneses P. Ultrasound therapy for recalcitrant diabetic foot ulcers: results of a randomized, double-blind controlled, multicenter study. *Ostomy Wound Manage* 2005;51(8):24-39.
- Enton MT, Brown KR, Seabrook GR, Towne JB, Cambria RA. A prospective randomized evaluation of negative-pressure wound dressings for diabetic foot wounds. *Ann Vasc Surg* 2003;17(6):645-9.
- Faglia E, Favales F, Aldeghi A, Patrizia C, Quarantiello A, Oriani G, Michael M, Capagnoli P, Morabito A. Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic foot ulcers. *Diabetic Care* 1996;19:1338-1343.
- Jeffcoate WJ, Harding KG: Diabetic foot ulcers. *Lancet* 2003; 361: 1545-1551.
- Gerdesmeyer L, Von Eiff C, Horn C, Henne M, Roessner M, Diehl P, Gollwitzer H. Anti-bacterial effects of extracorporeal shock waves. *Ultrasound in Medicine & Biology* 2005;31:115-9.
- Londahl M, Katzman P, Nilsson A, Hammarlund C, Sellman A, Wykman A, Hugo-Persson M, Apelqvist J. A prospective study: hyperbaric oxygen therapy in diabetics with chronic foot ulcers. *Journal of Wound Care* 2006; 15(10):457-9.
- Macfarlane RM, Jeffcoate WJ: Factors contributing to the presentation of diabetic foot ulcers. *Diabet Med* 1997; 14(10): 867-870.
- Robson MC, Phillips LG, Thomason A, Altrock BW, Pence PC, Hegggers JP, Johnston AF, McHugh TP, Anthony MS, Robson LE, et al. Recombinant human platelet-derived growth factor-BB for the treatment of chronic pressure ulcers. *Ann Plast Surg* 1992;29 (3):193-201.
- Ruffieux P, Hommel L, Saurat JH: Long-term assessment of chronic leg ulcer treatment by autologous skin grafts. *Dermatology* 1997; 195: 77-80.
- Schaden W, Thiele R, Kolpl C, Pusch M, Nissan A, Attinger C, Maniscalco-Theberge ME, Peoples GE, Elster EA, Stojadinovic A. Shock wave therapy for acute and chronic soft tissue wounds: A feasible study. *J Surgical Research* 2007;143(1): 1-12.
- Schaper NC, Apelqvist J, Bakker K: The international consensus and practical guidelines on the management and prevention of the diabetic foot. *Current Diabetes Reports* 2003; 3(6): 475-479.
- Wang CJ, Huang HY, Pai CH: Shock wave enhances neovascularization at the tendon-bone junction. *J Foot and Ankle Surg* 2002; 41 (1): 16-22.
- Wang CJ, Kuender Yang, Wang FS, Huang CC Yang LJ: Shock wave induces neovascularization at the tendon-bone junction. A study in rabbits. *J Orthop Res* 2003; 21:984-989.