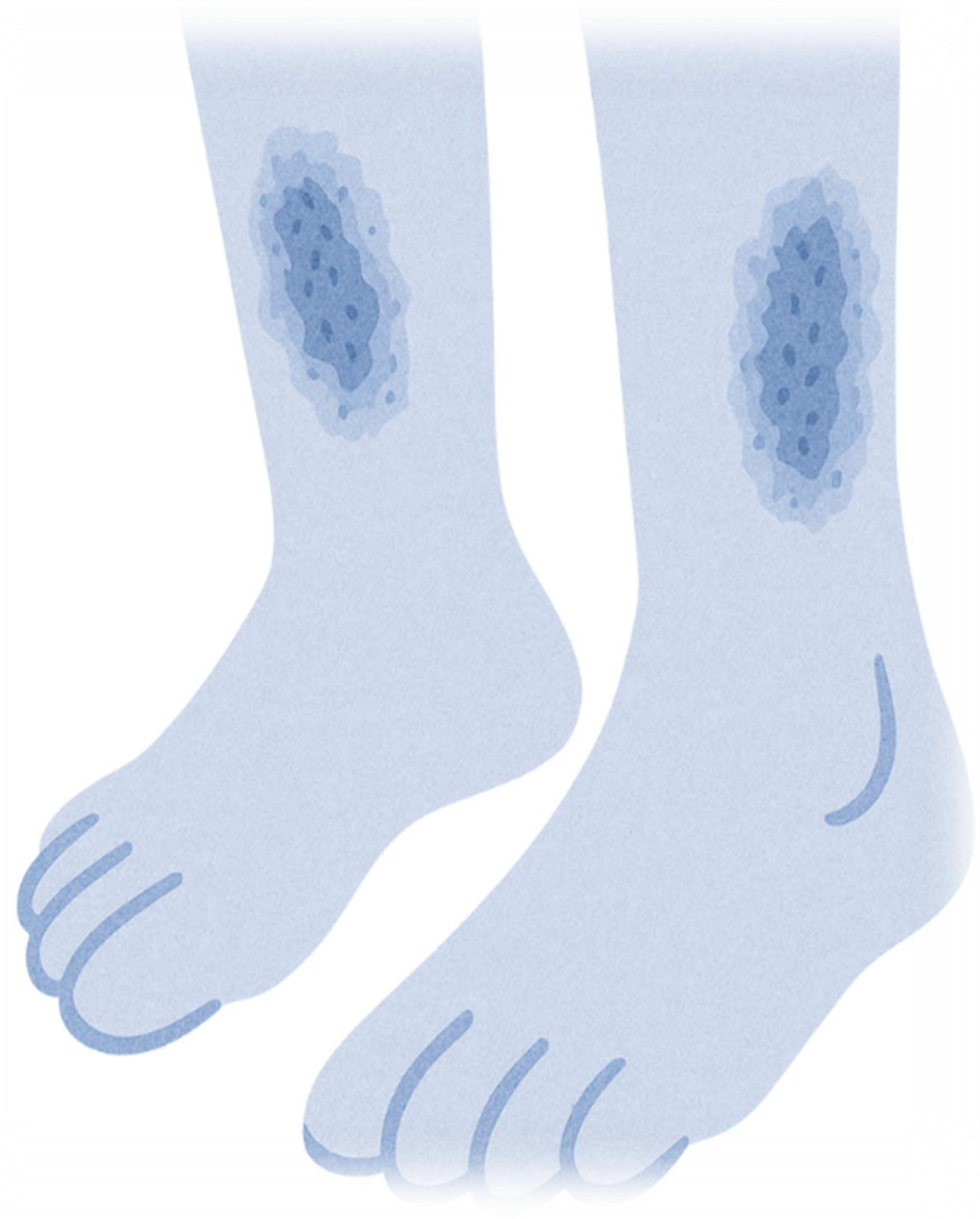


MoreNova- Vascular Diseases

PAD- Peripheral Arterial Disease

WH- Wound Healing

A Compendium of Research Articles on shock wave therapy and on Integration of MoreNova into Vascular Diseases

MORENOVA

Table of Contents

Learn from Leading Practitioners

This compendium lists selected publication references, synthesizing the knowledge and experiences from leading practitioners, and documenting a range of applications and models for implementing MoreNova in routine practice.

- We hold ourselves to a high standard when it comes to accumulating clinical evidence
- We are committed to extending research opportunities to medical professionals worldwide
- We strive to engage the professional community to explore existing guidelines in order to reach knowledge-based consensus recommendation for change, while recognizing the valued relationship between physiotherapists and industry

To learn more about how MoreNova can benefit you and your patients, please contact us at:


https://initiamedical.com


info@initiamedical.com

MoreNova at a Glance

MoreNova is a new-generation shockwave-based non-invasive treatment designed to promote wound healing and address the challenges of Peripheral Artery Disease (PAD) across various patient populations. MoreNova is equipped with an innovative hands-free arm that enhances patient comfort while optimizing clinician workflow. Its proprietary shockwave technology combines broad tissue coverage with deep penetration, providing fast and effective outcomes for conditions requiring enhanced angiogenesis and tissue regeneration, including those affecting circulation and wound closure.

Clinical Indications for Utilizing MoreNova

Indications in vascular diseases:

- PAD
- venous leg ulcers
- diabetic foot ulcers
- pressure sores

Clinical benefits:

- Low- to zero-risk, no heating, no ablation, no side effects
- High safety and efficacy across various indications/ages
- Clinically validated regenerative effect
- Multiple health indications
- Non-surgical, non-pharmacological
- Improved patient compliance
- Low interoperator variability
- Durable results

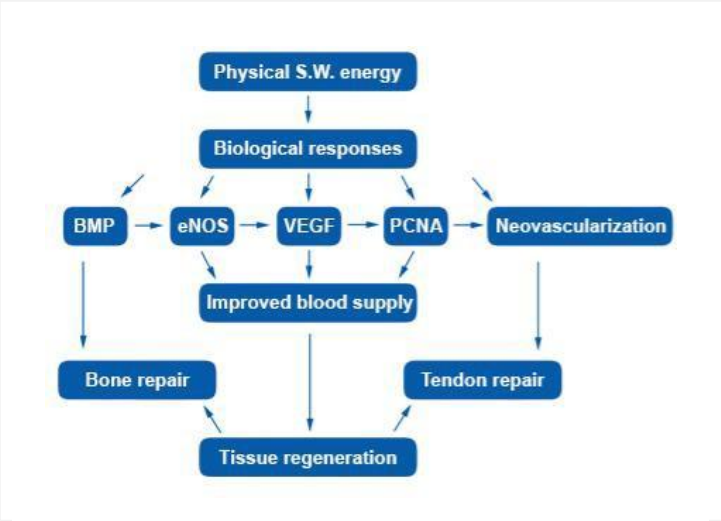
Features and highlights

- Proprietary Large-Area Shockwave Technology (LAST) electromagnetic technology
- Optimal comfort: outpatient setting, anesthetic-free, quick and painless
- Time efficient: no preparations, no downtime, no recovery time
- Fits in standard workflow, requires no additional equipment
- Noticeable results directly after the first few sessions
- Exclusive hands-free application
- Straight-forward procedure

Molecular Mechanism of Action

Shockwaves are characterized by jump change in pressure, high energy peak, high amplitude and non-periodicity. The energy is transferred to the transmitter at the end of the applicator and further into the tissue.

Our bodies have a remarkable capacity to heal themselves. Low Intensity Shockwave Therapy (LISWT) augments the body's natural cellular repair mechanisms, using acoustic pressure waves which carry low-intensity energy to tissues. The cascade of biological actions that follows LISWT leads to accelerated tissue regeneration and cell growth, and is able to restore, improve, and even normalize tissue form and function.



Wang CJ, Wang FS, Yang KD,
Biological mechanism of musculoskeletal shockwaves
ISMST Newsletter 2006, 1 (I), 5-11

During and after treatment, LISWT delivers pulse waves, stimulating the following regenerative and reparative processes simultaneously:

- ANGIOGENESIS AND NEOVASCULARIZATION

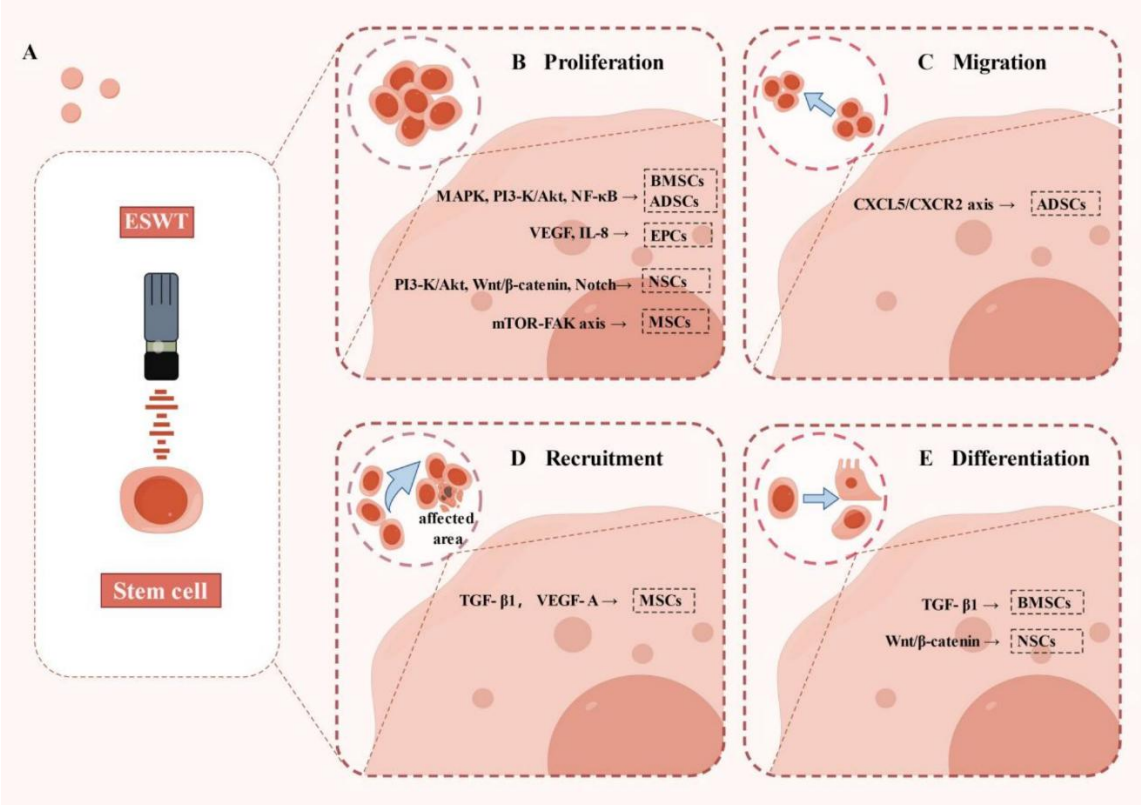
  Nutrient blood supply and tissue oxygenation are vital to initiate and maintain the healing processes of damaged tissue structures. By causing capillary microruptures in the tissue, LISWT stimulates the recruitment of platelets and the subsequent increased expression of growth factors, which in turn activate the propagation and formation of new blood vessels.

- RECRUITMENT AND ACTIVATION OF MESENCHYMAL STEM CELLS (MSCs)

  ESWT stimulates stem cells within the body and enhances their ability to repair damaged tissue. This is achieved by activating several key biological processes:

- Proliferation - the shockwaves encourage stem cells to multiply, increasing the number of cells available for tissue repair.
- Differentiation - stem cells are guided to transform into specific types of musculoskeletal cells, such as tendon cells, bone cells, or cartilage cells, depending on the area being treated.
- Migration and Recruitment - ESWT signals stem cells to move toward the injured tissue, where they accumulate and initiate regeneration.

These effects are mediated through activation of cellular signaling pathways, such as MAPK, PI3K/Akt, and NF-κB, which are known to regulate tissue healing and regeneration.



♦ DECALCIFICATION OF PLAQUES AND ARTERIAL REMODELLING

Vascular and fibrocellular tissue calcification commonly result from repetitive stress, microtrauma and aging. Calcium build-up can lead to histologic and structural changes, reduce tissue elasticity and impact vessel hemodynamics. LISWT-induced shear stress breaks up fibrosis and existing calcifications, leading to fragmentation of calcium deposits into granular particles, which are then removed by the lymphatic system.

- STIMULATION OF COLLAGEN PRODUCTION AND RESTRUCTURING

  Collagen plays an important role in maintaining the integrity of myoskeletal and ligamentous structures. LISWT accelerates collagen synthesis and deposition, forming denser and stiffer fibers, and creating a firmer structure.

- REVERSAL OF CHRONIC INFLAMMATION

  Mast cells are the foundation of inflammatory response, wound healing and defence against pathogens. LISWT increases Mast cell activation, followed by the production of chemokines and cytokines. initially enhancing the inflammatory process, these pro-inflammatory compounds ultimately allow for halting of chronic inflammation conditions and associated pain.

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Extracorporeal shockwave therapy as a novel treatment for Intermittent Claudication[1]

Mr. Paris Limin Cai

Background - Intermittent claudication is a prevalent manifestation of peripheral arterial disease and affects about 3% of the UK population. Its conservative management includes best medical therapy, smoking cessation and supervised exercise, however exercise uptake among patients is poor. Pilot data has demonstrated that extracorporeal shockwave therapy is effective for improving walking distance in patients with intermittent claudication. The work of this thesis aims to consider its effectiveness for improving quality of life.
Methods - In a double-blind, sham-controlled, randomised trial, patients with intermittent claudication were randomised in a 1:1 ratio to extracorporeal shockwave therapy or sham treatment. The primary endpoint was change in physical functioning at 12-week follow-up, as measured by the SF-36. Secondary endpoints included changes in walking distances, and changes in ankle brachial pressure index pre and post exercise, amongst others.
Results - 138 patients were recruited and randomised. The intervention group had a significantly higher physical functioning score at 12 weeks (Mdn 41 vs 34, p=0.033), though not significant at secondary analysis. They also had significantly longer claudication distance (Mdn 125 vs 88, p=0.004) and maximum walking distances (Mdn 179 vs 129, p=0.013). No significant difference in ABPI between the two groups was evident.
Conclusion - This study demonstrates that extracorporeal shockwave Therapy is clinically effective for improving walking distances and may have a positive effect in quality of life in patients with intermittent claudication. It should be considered as an adjunct to conservative management, especially in patients not willing or unable to participate in supervised exercise programs.

Shockwave therapy in patients with peripheral artery disease[2]

Marco Matteo Ciccone , Angela Notarnicola, Pietro Scicchitano, Marco Sassara, Santa Carbonara, Mariagrazia Maiorano, Biagio Moretti

Introduction: Previous studies support the fact that extracorporeal shockwave (SW) induces angiogenesis and improves symptoms in patients affected by limb ischemia. The aim of this study was to evaluate the effects of SW therapy in patients with peripheral artery disease (PAD).
Methods: Twenty-two patients were enrolled in this study and were randomly assigned into two groups: SW treatment (12 patients, 67 ± 9 years) and control (10 patients, 68 ± 12 years). The inclusion criteria were the following: age over 40 years, PAD diagnosis, optimal medical therapy, and ankle-brachial index less than 0.9. SW therapy was administered using the Minilith® SL1 litotriptor with an ultrasound guide able to detect the target area using a B-mode technique and a 7.5 MHz convex probe emitting 2,000 impulses with an energy flux density of 0.03 mJ/mm(2).
Results: The variation in the degree of stenosis before and after treatment was statistically significant between the groups (-9% ± -10% vs. 0% ± 0%; P = 0.001). In addition, a significantly higher number of treated patients than controls showed a reduction in the Fontaine stage (12 [63%] vs. 0 [0%]; P < 0.001). This result was confirmed by analyzing the difference in patients' pain-free walking distance before and after SW therapy (76 ± 46 m vs. 0 ± 0 m for treated patients vs. controls; P < 0.001) and the difference in pain severity (measured on a pain scale; -1.4 ± 0.5 in the treated patients vs. -0.2 ± 0.4 in the controls; P < 0.001).
Conclusion: On the basis of these results the authors hypothesized a direct effect of SW on the ultrastructural composition of the vessel walls, inducing a reduction in artery stenosis. These data support the application of SW therapy as a new medical tool to improve the natural clinical course of PAD.

Extracorporeal Shock Wave Therapy Improves the Walking Ability of Patients With Peripheral Artery Disease and Intermittent Claudication[3]

Fukashi Serizawa; Kenta Ito; Keiichiro Kawamura; Ken Tsuchida; Yo Hamada; Tsutomu Zukeran; Takuya Shimizu,Daijiro Akamatsu; Munetaka Hashimoto; Hitoshi Goto; Tetsuo Watanabe ; Akira Sato; Hiroaki Shimokawa; Susumu Satomi

Background: Despite the recent advances in bypass surgery and catheter interventional therapy for peripheral artery disease (PAD), the long-term outcome of revascularization therapy for infrapopliteal lesions remains unsatisfactory. We have previously demonstrated that low-energy extracorporeal shock wave (SW) therapy effectively induces neovascularization through upregulation of angiogenic factors and improves myocardial ischemia in pigs and humans and in hindlimb ischemia in rabbits. In this study, we thus examined whether our SW therapy also improves the walking ability of patients with PAD and intermittent claudication.
Methods and Results: We treated 12 patients (19 limbs) in Fontaine II stage (males/females, 10/2; 60–86 years old) with low-energy SW therapy to their ischemic calf muscle 3 times/week for 3 consecutive weeks. After 24 weeks, the pain and distance subscale scores of the walking impairment questionnaire were significantly improved (33±25 vs. 64±26, 27±16 vs. 64±23, respectively, both $P<0.01$). Maximum walking distance was also significantly improved at 4 weeks (151±37% from baseline, $P<0.01$) and was maintained at 24 weeks (180±74% from baseline, $P<0.01$). Moreover, the recovery time of the tissue oxygenation index in the calf muscle during a treadmill test, which reflects local O2 supply, was significantly shortened (295±222 s vs. 146±137 s, $P<0.01$). Importantly, no adverse effects were noted.
Conclusions: Non-invasive SW therapy improves the walking ability of PAD patients. (Circ J 2012; 76: 1486 – 1493)

Evaluation of the Effects of Extracorporeal Shockwave Therapy in Patients With Peripheral Arterial Disease: A Meta-Analysis of Randomized Control Trials[4]

Zaid Munir , Muhammad Akash , FNU Jaiprada , Bilal Abu Tarboush , Osama Ijaz , Anan Bseiso , Sujith K. Palleti , Adil Amin

Background:
Peripheral arterial disease (PAD) is a major cause of morbidity and impaired quality of life, often leading to leg pain on walking (claudication). Traditional treatments include medication, exercise therapy, and invasive procedures, but not all patients respond or can participate in existing therapies. Extracorporeal shockwave therapy (ESWT), already used in other medical conditions, has emerged as a non-invasive alternative to potentially improve symptoms and blood flow in PAD patients.
Methodology: A meta-analysis was conducted according to PRISMA guidelines. Systematic searches of PubMed, EMBASE, and Cochrane databases identified randomized controlled trials (RCTs) assessing ESWT in patients with PAD. Four RCTs (total 228 patients) were included. Main outcomes: changes in maximum walking distance (MWD), pain-free walking distance (PFWD), ankle-brachial index (ABI), and arterial stenosis.
Results:

- Improvement in Walking Distances: ESWT significantly improved both pain-free walking distance and maximum walking distance compared to controls.
- No Significant Change in ABI: ESWT did not significantly change the ankle-brachial index, a measure of macrovascular blood flow.
- Reduction in Arterial Stenosis: In one study, ESWT reduced arterial stenosis significantly more than controls.
- Heterogeneity: Noted high variation between studies but results regarding walking improvement were consistent and significant.

Conclusions:
ESWT is effective in increasing pain-free and maximum walking distances and in reducing arterial stenosis in PAD patients, though it does not significantly impact ABI scores. These results suggest ESWT benefits microvascular rather than macrovascular function. As a safe, non-invasive therapy, ESWT may be a valuable addition for PAD patients- especially those unable or unwilling to undergo supervised exercise or invasive procedures. Further large-scale studies are needed to confirm long-term safety, efficacy, and cost-effectiveness.

Novel Large Area Electromagnetic Shockwave Therapy treats successfully a serious DFU wound.[5]

Dr. Dror Robinson; Dr. Mustafa Yassin

Background: A collaboration with Rabin Medical Center focused on serious, chronic diabetic foot ulcers using the Morenova therapy protocol (low-intensity shock waves).
Methodology: Ten chronic DFU patients were initially treated according to Morenova protocol. Treatment involved twice-weekly shockwave therapy sessions.
Results:

Patient Case 1:

- Initial wound area: 607 mm^2.
- 22 sessions over 11½ weeks resulted in complete closure and re-epithelialization.
- Physicians reported high effectiveness of therapy.

Figure 1: Documentation of wound condition throughout shockwave therapy - patient 1

Patient Cases 2-5:

- Rapid wound closure documented in timeframes ranging from two weeks to one month.
- Sequential evaluations after individual and multiple sessions showed continuous progression and healing.

Figure 2: Documentation of wound condition throughout shockwave therapy - patient 2

Figure 3: Documentation of wound condition throughout shockwave therapy - patient 3

Figure 4: Documentation of wound condition throughout shockwave therapy - patient 4

Figure 5: Documentation of wound condition throughout shockwave therapy - patient 5

All cases demonstrated significant wound area reduction or full closure with short-term shockwave intervention.

Conclusions:

Low-intensity shockwave therapy, as applied via Morenova protocol, was highly effective for chronic diabetic foot ulcers in Rabin Medical Center's cohort, often achieving complete healing within weeks even in challenging cases.

Case Studies – Ichilov Hospital – Low-Intensity Shock Waves for Diabetic Foot Ulcer (DFU)[5]

Background: Ichilov Hospital was selected as a beta site to assess wound healing using low-intensity shock wave technology in patients with various types of diabetic foot ulcers.
Methodology: Multiple patient cases were documented; each involved regular shockwave therapy sessions. Safety and treatment efficiency were recorded.
Results:

Patient Case 1:

- Treated from Day 1 to Day 77.
- Substantial wound reduction and healing observed over the treatment period.

Figure 6: Documentation of wound condition throughout shockwave therapy – Patient 1

Patient Case 2:

- Five sessions within 18 days; marked wound improvement.

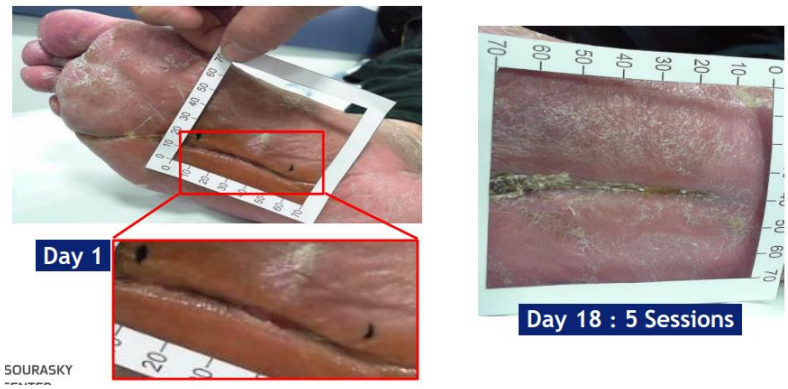

Figure 7: Documentation of wound condition throughout shockwave therapy – Patient 2

Patient Case 3:

- Six sessions over 22 days; wound progression tracked with photographic evidence.

Figure 8: Documentation of wound condition throughout shockwave therapy – Patient 3

In all cases, sequential images demonstrated significant wound healing with repeated shockwave sessions.

Conclusions:

Low-intensity shockwave therapy facilitated marked acceleration of healing in diabetic foot ulcers at Ichilov Hospital, with demonstrated safety and efficacy across multiple cases.

Low Intensity Shockwave Treatment Modulates Macrophage Functions Beneficial to Healing Chronic Wounds[6]

Jason S. Holsapple, Ben Cooper, Susan H. Berry, Aleksandra Staniszewska, Bruce M. Dickson,Julie A. Taylor, Paul Bachoo and Heather M. Wilson

Background: Chronic wounds, such as venous ulcers, are challenging to heal and are characterized by stalled inflammation, dysfunctional macrophage activity, impaired angiogenesis, and persistent tissue damage. Extracorporeal shockwave therapy (ESWT) is clinically used for its regenerative effects, but the underlying mechanisms, particularly regarding macrophage function, are not well understood.

Methodology:

- Patients: Biopsies were taken from nine patients with non-healing venous ulcers before and two weeks after a single round of ESWT.
- In Vivo: Wound healing was evaluated (wound area measurement, histological and immunohistochemical analyses for angiogenesis, macrophage numbers, and activation).
- In Vitro: Macrophage cultures were treated with clinically relevant shockwave parameters. Functional assays included phagocytosis (of apoptotic cells and beads), viability, cytokine/growth factor gene expression, and signaling pathway activation.

Results: In Vivo:

- ESWT improved wound healing in most patients (~78%).
- Wounds showed increased angiogenesis (CD31 staining) and reduced macrophage density post-ESWT.
- Macrophage activation increased post-treatment, regardless of M1/M2 phenotype.

In Vitro:

- Shockwave exposure increased macrophage phagocytosis of apoptotic cells (not beads), suggesting specificity.
- Enhanced gene expression of healing-related cytokines and growth factors (TNF, IL-1, PDGF, TGFβ).
- Morphological changes suggested greater macrophage activation.
- ERK signaling was upregulated, implicating mechanotransduction as a pathway.

Conclusions: Low-intensity shockwave therapy improves healing of chronic wounds by modulating macrophage function- specifically by enhancing activation, boosting the clearance of apoptotic cells, and increasing production of healing mediators, partly via ERK pathway activation. ESWT thus acts as an important physical stimulus promoting wound resolution and may have potential for other macrophage-driven disorders.

Prospective Randomized Trial of Accelerated Re-epithelization of Skin Graft Donor Sites Using Extracorporeal Shock Wave Therapy[7]

Christian Ottomann, Bernd Hartmann, Josh Tyler, Heike Maier, Richard Thiele, Wolfgang Schaden, Alexander Stojadinovic

Background: Extracorporeal shock wave therapy may enhance revascularization and repair of healing soft tissue.
Methodology: Between January 2006, and September 2007, 28 patients with acute traumatic wounds and burns requiring skin grafting were randomly assigned in a 1:1 fashion to receive standard topical therapy (nonadherent silicone mesh [Mepitel, Mölnlycke Health Care] and antiseptic gel [polyhexanide/octenidine]) to graft donor sites with (n = 13) or without (n = 15) defocused extracorporeal shock wave therapy (ESWT, 100 impulses/cm2 at 0.1 mJ/mm2) applied once to the donor site, immediately after skin harvest. The randomization sequence was computer generated, and the patients were blinded to treatment allocation. The primary endpoint was time to complete donor site epithelialization and was determined by an independent blinded observer.
Results: Statistical tests indicated no unbalanced distribution of subject characteristics across the two study groups. Mean times to complete graft donor site epithelialization for patients who did and did not undergo ESWT were 13.9 2.0 days and 16.7 2.0 days, respectively (p = 0.0001).

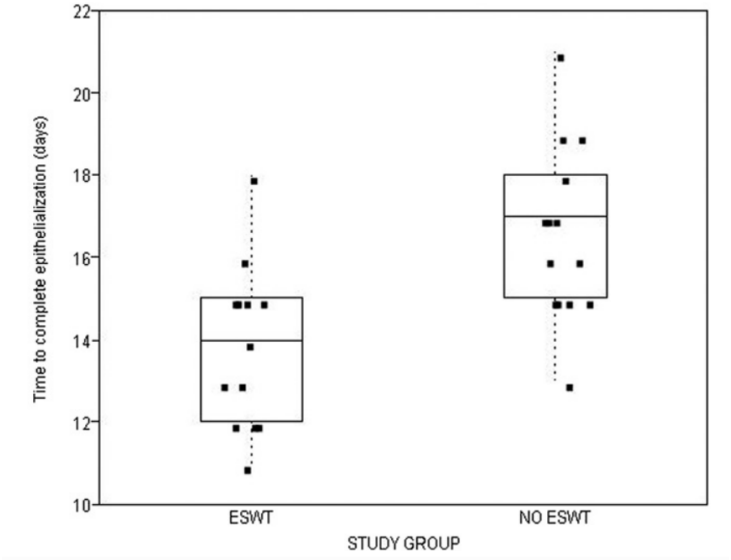

Figure 9 : Time to complete split thickness skin graft donor site

Conclusions: For centers that apply nonadherent gauze dressings and topical antiseptics to skin graft donor sites, application of a single defocused shock wave treatment immediately after skin graft harvest can significantly accelerate donor site epithelialization. (J Am Coll Surg 2010;211:361–367. © 2010 by the American College of Surgeons).

Extracorporeal Shock Wave Therapy for Treating Foot Ulcers in Adults With Type 1 and Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials[8]

Qiangru Huang; Peijing Yan; Huaiyu Xiong; Tiankui Shuai; Jingjing Liu; Lei Zhu; Jiaju Lu; Xiue Shi; Kehu Yang g ; Jian Liu

Background: Diabetic foot ulcers (DFUs) are a common and challenging complication among diabetic patients, often leading to poor outcomes like non-healing wounds, infection, and amputation. Despite various standard wound care approaches, there's a critical need for effective adjunct therapies. Extracorporeal shock wave therapy (ESWT) is a novel non-invasive treatment showing promise in accelerating healing for chronic wounds, including DFUs.

Methodology: A systematic review and meta-analysis of randomized controlled trials (RCTs) following PRISMA guidelines. Eight RCTs (N = 339) included, comparing ESWT plus standard wound care (SWC) to SWC (or SWC plus hyperbaric oxygen therapy [HBOT]) in adults with type 1 or type 2 diabetes and active foot ulcers. Main outcomes: reduction in wound surface area (WSA), percentage of re-epithelialization, complete cure rate, population of unchanged ulcers, and adverse events. Data extraction and quality assessment followed Cochrane guidelines.

Results:

- WSA Reduction: ESWT led to a greater reduction in wound surface area (by 1.54 cm^2 at follow-up).
- Re-epithelialization: Increased by 26.3% with ESWT at follow-up.
- Complete Cure Rate: ESWT doubled the chances of complete ulcer cure at end of treatment (risk ratio = 2.22) but showed no statistically significant difference at extended follow-up.
- Treatment Ineffectiveness: ESWT reduced the risk of ineffective treatment by 4.8-fold versus control.
- Superiority over HBOT: ESWT outperformed HBOT regarding both complete cure rate and reduction in unchanged ulcers.
- Wound Healing Time: ESWT shortened healing time by 19 days (in studies reporting this outcome).
- Safety: No serious adverse events; ESWT was well tolerated with only mild and transient side effects.

Conclusions: ESWT is a feasible, safe, and effective adjunct therapy for diabetic foot ulcers. It significantly accelerates healing, improves complete cure rates, and reduces treatment failures, showing better outcomes than standard care or hyperbaric oxygen therapy alone. Further robust RCTs are needed to clarify early-stage effects, long-term outcomes, and cost-effectiveness, but ESWT offers a promising option for the clinical management of intractable and recurrent DFUs.

Randomized Clinical Trial Prospective Randomized Phase II Trial of Accelerated Reepithelialization of Superficial Second-Degree Burn Wounds Using Extracorporeal Shock Wave Therapy[9]

Christian Ottomann, Alexander Stojadinovic, Philip T. Lavin, Francis H. Gannon, Michael H. Heggeness, Richard Thiele, Wolfgang Schaden and Bernd Hartmann.

Background: As extracorporeal shock wave therapy (ESWT) can enhance healing of skin graft donor sites, this study focused on shock wave effects in burn wounds.
Methods: A predefined cohort of 50 patients (6 with incomplete data or lost to follow-up) with acute second-degree burns from a larger study of 100 patients were randomly assigned between December 2006 and December 2007 to receive standard therapy (burn wound debridement/topical antiseptic therapy) with (n = 22) or without (n = 22) defocused ESWT (100 impulses/cm2 at 0.1 mJ/mm2) applied once to the study burn, after debridement. Randomization sequence was computer-generated, and patients were blinded to treatment allocation. The primary endpoint, time to complete burn wound epithelialization, was determined by independent, blinded-observer. A worst case scenario was applied to the missing cases to rule out the impact of withdrawal bias.
Results: Patient characteristics across the 2 study groups were balanced (P > 0.05) except for older age (53 ± 17 vs. 38 ± 13 years, P = 0.002) in the ESWT group. Mean time to complete (≥95%) epithelialization (CE) for patients that did and did not undergo ESWT was 9.6 ± 1.7 and 12.5 ± 2.2 days, respectively (P < 0.0005). When age (continuous variable) and treatment group (binary) were examined in a linear regression model to control the baseline age imbalance, time to CE, age was not significant (P = 0.33) and treatment group retained significance (P < 0.0005). Statistical significance (P = 0.001) was retained when ESWT cases with missing follow-up were assigned the longest time to CE and when controls with missing follow-up were assigned the shortest time to CE.
Conclusions: In this randomized phase II study, application of a single defocused shock wave treatment to the superficial second-degree burn wound after debridement/topical antiseptic therapy significantly accelerated.

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info@initiamedical.com • www.initiamedical.com

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