ISMST

Newsletter

MAY 2011
VOLUME 7, ISSUE 1

Editorial · Editorial comments

Ludger Gerdesmeyer

Dear Friends and Colleagues,

On behalf of the ISMST Organization committee, I have the pleasure and privilege to invite you to the 14th ISMST Congress that will be held in Kiel, Germany, on the 9th-11th June 2011.

The ISMST is the world's largest organization with regards to medical shock wave treatment.

The broad field of shockwave treatment has been expanding rapidly world wide. Standard indications including musculo-skeletal disorders and bone pathologies such as non-union, avascular necrosis and tendon pathologies will be presented. Due to the biological principles of shockwaves multiple new indications have developed. Recent research, scientific updates and preliminary results in skin lesions, myofascial treatment and nerve injuries will be part of the conference as well as instructional hands-on courses. International experts will talk about shoulder, foot, pain, sports and tendon injuries, technical developments, how-to-use-shockwaves and financial aspects.

The Instructional courses consisting of part 1 and 2 are certified by the ISMST and the DIGEST.

The conference venue is the Atlantic hotel right in the centre of Kiel, which is know as Germany´s sailing city with all kinds of yachts, boats and large luxury cruise ships, nice weather, famous beaches, and many other attractive options of entertainment.

I look forward to welcoming you to Kiel

Ludger Gerdesmeyer

Richard Thiele, MD
Member of the ISMST Supervisory Board

Dear Colleagues Across the World,

This is now the 7th issue of the ISMST newsletter, published annually in conjunction with the ISMST conference.

Once again a heartfelt thanks to Dr. Paulo Roberto dos Santos in Brazil from the ISMST board of directors. The ISMST newsletter publishes the study findings, basic research and views of scientists we consider most relevant to the ISMST community. The newsletter with a print run of 3,000 can as well be downloaded directly from our Website. The articles published in the newsletter do not necessarily reflect the opinions of the ISMST community, but are specifically the views of their respective authors.

As you have no doubt noticed, not only evidenced-based studies are presented but also the intriguing science-based opinions and statements of individual researchers and scientists. They are intended to stimulate discussion and spur further research and investigation.

We would like to again point out the guidelines for the proper application of ESWT, which can be viewed on the new Website of the German Shockwave Therapy Association (DIGEST, www.digest-ev.de). These guidelines are constantly revised to accommodate the latest scientific findings and knowledge. At the meeting of the council of experts in January of this year, it was decided that the parameters to be published in the guidelines be adopted as the official parameters, which are drawn from published evidence-based studies. These parameters will vary according to device and method of shockwave generation. No certifiable parameters will be issued in the guidelines for individual indications requiring individual devices for which no previous studies exist. The parameters moreover are biometrically worked out before being incorporated into the guidelines. When completed, the guidelines will become the basis for ESWT treatments and their subsequent billing, primarily in the German-speaking countries and later worldwide.

For this reason, it is essential to continue carrying out and compiling scientific studies and to present them at conferences and in scientific journals, so that knowledge on the efficacy of ESWT can be further accrued and their future funding ensured. ESWT must remain in the hands of medical doctors and physicians, otherwise development of this wonderful therapeutic method will risk ceasing and coverage by insurers risk being denied. Focused EWST has too many benefits, and is ultimately too dangerous, to be left in the hands of non-medical personnel, who will treat it as just another electro-medical technology.

We look forward to the continual development of shockwave therapy in the fields of bone treatment, cardio-surgery and skin ailments. The emphasis of this particular newsletter is the treatment of skin ailments and myofascial pain syndrome

We hope you will enjoy both the articles and this year's conference in Kiel.

Yours,

Richard Thiele

Inside this Issue

EPAT for Trigger Points and Myofascial Conditions in Sport Medicine

Robert GORDON, M.D.

Chris Broadhurst, M.D.

Introduction

EPAT (Extracorporal Pulse Activation Therapy) is used to describe the application of radial pressure waves, sometimes also referred to as radial shock waves. For the application of focused shockwave is the term ESWT most common. EPAT and ESWT can be used to treat the musculo-skeletal complex effectively. The application of focused shockwaves applied to muscle trigger points are used for diagnostic and therapeutic purposes according to Dr. Gleitz (1). Manual examination of trigger points in combination with EPAT can be used for diagnostic and therapeutic purposes with positive results. In our practice, EPAT is used for the local treatment of muscular trigger point areas, tendon insertion pain and for smoothing of the myofascial structures. EPAT allows large muscle regions to be treated effectively and in a timely manner. The focused shock waves induce a reduction of nociceptive fibers whereas radial pressure waves (EPAT) seem to have a counter-irritation and pain modulating effect through GABAergic interneurons in the dorsal horn (1). In addition to this action, the pressure and vibrations of radial shock waves (EPAT) improve blood circulation and lymphatic drainage.

EPAT application to muscle trigger points, tendon insertion pain and myo-fascial conditions represents an evolution of use within the musculo-skeletal system. In our practice therapy is applied with an EPAT system developed by Storz Medical AG. The mode of action is identical to that used by pneumatic jack-hammers: that is a ballistic source (air compressor) generates pressure waves by means of a projectile impacting a solid applicator in the hand piece. The applicator (D-Actor with 20 mm diameter) has to be covered with coupling gel and then fixed in tight contact with the skin. The pressure used to drive the projectile can be varied continuously from 1 bar to 4 bar using a dial on the front panel of the control unit (2).

In our practice muscle shortening or tightness can be a risk factor for tendinosis. Reducing the tension within the Musculo-Skeletal Complex can lead to a reduction in pain. A complete Functional Movement Screen (3) and Clinical Orthopaedic Examination (4) will be performed before an EPAT treatment is initiated.

1. The effectiveness of EPAT on the muscle belly might be given by the trigger point therapy theory established by Travell and Simons work (5). The presence of trigger points in muscles cause a significant motor dysfunction with the clinical findings of a restriction of full stretch motion, a palpable increase in muscle tenseness and painful contraction knots. The contracture of the actin-myosin filaments caused by trigger points, due to the energy crisis of the motor end-plate, leads to muscle contractures which result in a measurable overall shortening of the affected muscles and a limitation in joint range of motion.

2. The effectiveness of EPAT on the tendon insertion or the tenoperiosteal junction might be given by a transverse friction technique that was developed by Dr. James Cyriax (4). The scar tissue or thickening is broken up by counter pressure of the EPAT head with a sweeping motion moving in a transverse direction across the tendon.

3. The effectiveness of EPAT on the myofascial meridian system as described by Thomas W. Myers in Anatomy Trains (6) can be shown through the use of EPAT smoothing in the direction of connection. Once the particular patterns of these myofascial meridians are recognized and the connections understood, they can be applied in EPAT smoothing treatment.

The use of EPAT has also been shown to have promising results in improving local circulation (reactive hypermia) and reduce the concentration of vasoneuro-active substances within the generalized treatment area (2).

EPAT Treatment Guidelines of the Shoulder Musculo-Skeletal Complex:

The goal is to reduce muscle shortening in the musculo-skeletal complex

The driving pressure (bars) is adjusted to the patient's pain threshold

500-1000 Pulses Decreases TP within muscle belly or musclo-tendinous junction

1000-1500 Pulses Decreases insertion scar tissue or thickening

1000-2000 Pulses myofascial meridian smoothing

Therapy frequency of one session per 3-10 days has been shown to be ideal.

EPAT Suggested Treatment Areas for Shoulder Pain:

2.6 Bars or decrease to patient tolerance 500-1000 Shocks + TP in Supraspinatus/ Infraspinatus	 
2.6 Bars or patient tolerance 500-1500 Shocks + Supraspinatus, Supine Lying	
3.0 Bars or patient tolerance 500-1500 Shocks + Infraspinatus, prone lying	
2.6 Bars or patient tolerance 500-2000 Shocks + Myo-fascial Meridian Smoothing	**Typical Complete Treatment: 2000-6000 Shocks @ ~11 Hz**

Post Treatment Recommendations:

- ☐ **Ice:** Not to be used as it will affect the local circulation (reactive hypermia)
- ☐ **Heat:** To aid in circulation
- ☐ **Myofascial Release Techniques/ Active Stretching:** ↓ tissue memory

Symptoms Should Improve Within 1-2 Treatments
Symptoms Should Resolve within 1-6 Treatments.

The common result of treatment is a reduction of muscle tone along with a diminished extent of muscle shortening, improved mobility and pain reduction. EPAT for treating muscle shortening needs continued clinical protocols to be established for therapeutic benefit. EPAT shows promising results in a non-invasive solution to accelerate the recovery from Trigger Points and Myofascial conditions (7). We look forward to the future of EPAT and it's integration into the Sport Medicine field and the development of powerful integrative therapeutic strategies.

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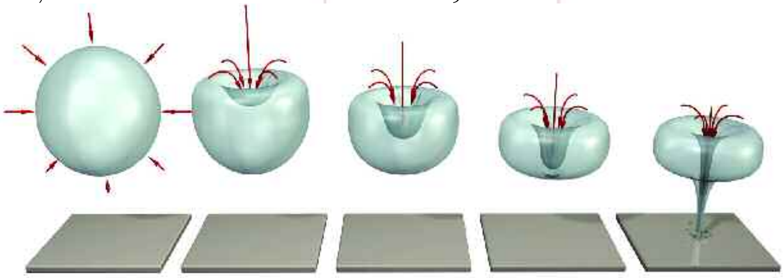
What is cavitation? Destructive or useful

Lose fat without effort - this is what an increasing number of therapists promise to achieve with the help of a new generation of ultrasound systems that use the so-called cavitation technology. The question is, what do these systems really accomplish: cavitation, degassing, heat, or simply everything?

Physics defines cavitation as a local vaporisation of water molecules due to strong pressure changes. The tensile components of these pressure changes, caused during lithotripsy for instance, tear the water molecules successively apart (vaporisation). The cavities generated by this process are cavitation bubbles, and the result of this sudden imbalance is a spontaneous implosion of the cavitation bubble. This spontaneous collapse produces a local shock wave or causes microjets. Cavitation requires high negative pressures (Herbert et al., 2006: between 260 bar and 170 bar).



((Bildunterschrift: Creation of a micro-jet: Cavitation bubbles near obstacles cannot collapse in a spherically symmetrical way, since the obstacle hampers the flow of the fluid. This causes the development of micro-jets that hit the interface at several hundred metres per second and lead to erosion or punch needle-like holes in vessels or membranes))

Bubble formation in an aqueous medium is referred to as noninertial or stable cavitation. Speaking purely physically, it has to be clearly differentiated from inertial cavitation because the bubbles generated in this way cannot collapse spontaneously, have a low energy level and decompose or dissolve slowly in the medium. Consequently, tissue damage caused by stable cavitation is highly improbable, which implies that effects on adipose cells are not to be expected.

So we have to distinguish between vaporising and degassing cavitation, the physical properties and cell-destructive effect of which are blatantly different. The extremely high forces resulting from microjets (see illustration) out of the collapse of the inertial cavitation bubble is not observed with noninertial or stable cavitation.

Devices having all the capabilities of what is sold as cavitation would have to be able to generate the extreme negative pressures described above. However, there is reason to fear that maybe not a single one of the »cavitation devices« on the market is capable of effecting cavitation in the proper physical sense described above. Therapeutic ultrasound, on the other hand, may cause local generation of heat, which may even result in cell destruction.

As a conclusion it can be said that in shock wave lithotripsy (ESWL), which works with high energy shock waves, cavitation exists and is useful. In the disciplines of Cardiac shock wave therapy (CSWT), Extracorporeal shock wave therapy (ESWT), and Acoustic Wave therapy (AWT®), which work with the application of low energy shock waves, cavitation does not exist and is not desired as cavitation in soft tissue can cause lesion.

Dr. Pavel Novak
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ESWT in Myofascial Pain Syndromes

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Introduction

Muscle pain is common and presents a major medical problem. As the understanding of its causes is still incomplete treatment options vary greatly. One of the latest and fastest spreading treatment approaches in Germany is the use of ESWT. For the last 10 years radial (r-ESWT) and focused (f-ESWT) shockwaves have been used systematically to treat myofascial trigger points (MTrP's), according to the trigger point theory of Travell and Simons (Travell & Simons, 1983).

Myofascial trigger points and muscle pain

The scientific understanding of muscle pain has changed within the last 30 years (Mense & Simons, 2001a). Muscle pain differs in many ways subjectively and objectively from pain in the skin or viscera. One of the most striking differences is the referral of pain into distant areas far away from the primarily irritated muscle nociceptors. This phenomenon of a "Referred Pain" is one of the characteristic and best known clinical sign of MTrP's and is explained by the "Convergence-Projection-Theory" (Ruch, 1949). Accordingly, nociceptive information is taking the wrong path in the spinal cord and is reaching somatotopically inappropriate dorsal horn neurons. The referred pain symptoms often lead patients to localize their pain incorrectly. In these cases, the physician must look for the actual source of the pain by exerting an external pressure during strong palpation of the muscle, and then treat it accordingly.

The myofascial trigger point is defined as a palpable local hardening of the muscle tissue that is painful on palpation and movement. According to a widespread hypothesis it is the result of a sarcomere contracture as a consequence of a dysfunctional neuromuscular endplate (Simons, 2004). The resulting local ischemia leads to a release of substances into the tissue that sensitize nociceptors (bradykinin, prostaglandin E2, serotonin), accounting for the tenderness of MTrP's to pressure. Substances of this type have been found within the MTrP's of patients (Shah et al., 2008). The nociceptors themselves release vasoactive neuropeptides (substance P, CGRP) that create a local neurogenic inflammation with hyperemia and edema, thus starting a vicious circle.

As clinical consequences MTrP's cause a significant motor dysfunction with a restriction of full stretch range of motion, a palpable increase in muscle tenseness and painful contraction knots.

For therapy a combination of deep friction massage and stretching is used. The following reasons for its effectiveness are discussed: Disconnection of actin-myosin links within the contracted sarcomeres, improvement in local circulation and the elimination of the ischemia-induced energy crisis (Mense & Simons, 2001a).

ESWT in muscles

The first publications about the successful use of focused shockwaves (f-ESWT) in muscular dysfunction described a diminution of pain (Kraus, Reinhart, Krause, & Reuther, 1999) and muscle tone (Lohse-Busch, Kraemer, & Reime, 1997). Since the year 2000 radial shockwaves (r-ESWT) are used and have become the more popular treatment tool (Bauermeister, 2003), (Gleitz, 2003). The basic idea about using shockwaves in muscles is the application of an external mechanical energy, comparable to the traditionally used technique of muscle knot compression ("Gelotrypsie") (Lange, 1931), followed by stretching exercises (Travell & Simons, 1983).

Although the mode of action of shockwaves on muscles has not been examined in detail, the following hypotheses are discussed, in analogy to the proven mechanisms in non-muscular tissues:

- Breaking Actin-Myosin-Links (Travell & Simons, 1983), (Shah et al., 2008)
- Hyperaemia + Neoangiogenesis (Wang, 2003), (Shah et al., 2008)
- Dilution of vasoneuroactive substances (Mense & Simons, 2001b), (Shah et al., 2008)
- Release of Substance P (Maier, Averbeck, Milz, Refior, & Schmitz, 2003), (Hausdorf, Lemmens, & Kaplan, 2008) and CGRP (Hong, 1994)
- Selective degeneration of C-fibers (Hausdorf, Lemmens, & Heck, 2008)
- Gate-Control-Theory (Wall & Cronly-Dillon, 1960), (Gregor & Zimmermann, 1972)
- Mechanotransduction (Neuland, Duchstein, & Mei, 2004), (Ingber, 2006)
- Release of NO (Neuland et al., 2004), (Mariotto et al., 2005)
- Muscle oscillation (Nazarov & Gorozhanin, 1988)
- Destruction of damaged fibers (Mense & Simons, 2001b)

Advantages and disadvantages of r-ESWT and f-ESWT in muscles

According to their physical characteristics radial and focused devices have different application profiles.

The advantages of the r-ESWT are the possibility of treating large muscle areas and the easy handling of the narrow hand piece. Its disadvantages are the reduced penetration depth (< 5 cm) and the diminished ability of provoking a referred pain, due to the radial (non-focused) wave propagation in the tissue.

The advantages of the f ESWT are the high reliability to provoke a referred pain pattern, due to focusing the energy in a small muscle area and the greater depth of penetration (> 5-10 cm). Its disadvantages are the small muscle area treated and the bulky, wide hand piece.

Treatment parameters with r-ESWT and f-ESWT

The r-ESWT is used for a local trigger point treatment and for a large area treatment ("smoothing"). The local treatment is done with 500-1000 impulses per trigger point at an intensity reaching a maximum pain level of VAS 8. The large area treatment is done at lower intensities and maximum pain levels (VAS 4) with 1000-4000 impulses, according to the seize of the muscle. The impulse frequency is chosen between 4 and 20 Hz. The treatments are scheduled 1-2/week for chronic pathologies and daily for acute injuries. 6-8 treatments are mostly needed.

The f-ESWT is used locally for diagnostic and therapeutic purposes. As the referred pain can be provoked regularly and easily, f-ESWT is first used to locate the deep trigger points within the muscle and then to treat them afterwards. 300-600 impulses are necessary per trigger point at an intensity of 0.05-0.35 mJ/mm^2 and an impulse frequency of 4 Hz.

Treatment intervals and the total number of treatments are identical to r-ESWT.

The choice of treatment intensity (mJ/mm² or bar) is made according to the following rules:

- Stay below pain threshold (<VAS 8)
- The higher the pain, the lower the energy
- Adapting the energy to patient's reaction after previous treatment
- Continuous increase in energy if possible

Combined treatment: f-ESWT and r-ESWT

The best results are achieved with the combination of both treatments: f-ESWT for the search and local treatment of MTrP's, followed by a "smoothing" large area treatment with r-ESWT.

Choice of muscles to be treated

The muscles are chosen according to the probability of containing MTrP's. With the knowledge about muscle specific referred pain patterns the description of pain by the patients gives already an idea of which muscles could be concerned.

The history about possible overload of the muscles (sport, trauma, posture, working position) makes the choice narrower. Finally the clinical examination with testing the range of motion (shortening), manual palpation and shockwave provocation of the referred pain that should be recognized by the patient confirms the choice.

Choice of treatment areas within the muscles

1. MTrP's, that fulfill all diagnostic criteria (Tender Spot, Taut Band, Referred Pain, Twitch Response)
2. Sensitive Pain Points with a strong local pain or a referred pain, that the patient recognizes
3. "Smoothing" area treatment of painful, tense and shortened muscles with r-ESWT

Examinations needed

As muscle pain is often seen in context with other pathologies outside the muscle (e.g. arthritis, radiculopathy, spinal and foraminal stenosis, neuropathy, myopathy, rheumatism, organ dysfunction, hormone dysregulation, psychiatric illness, infection, malnutrition, medicament induced) a differential diagnosis is needed.

For the local structural diagnostic a manual examination is imperative and an ultrasound examination is recommended. The ultrasound helps to measure the muscle thickness to choose the right focus for f-ESWT and allows identifying muscle pathologies such as tumors.

Empirically proven indications

Good results can be obtained in all acute or chronic muscle pathologies with pain, increased muscle tone and muscle shortening under the condition that there is no dominant pathology which irritates the muscle permanently or has structural damage to the muscle itself, such as

- Chronic neck pain with brachialgia, dorsalgia and cephalgia
- Periarticular shoulder pain and dysfunction
- Tendomyosis of the forearm extensor and flexor muscles without and with epicondylitis
- Dorsalgia
- Chronic low back pain without or with pseudosciatic irradiation
- Tendopathy and shortening of the adductor muscles
- Shortening of the quadriceps and hamstring muscles (chondropathia patella, jumper's knee)
- Peroneal and tibial muscle syndrome
- Shin Splint
- Shortening of the calf muscles without and with achillodynia
- Shortening of the plantar foot muscles without and with plantar fasciitis
- Metatarsalgia
- Sports injuries without discontinuity of the muscle

Side-effects

Under cautious and correct application no major side-effects can be seen.

A temporary increase in pain for 1-2 days is possible. Petechial bleedings are seen, especially with the r-ESWT after the first 2 treatments of the gluteal muscles.

Contraindications

The following structures should not be in the focus of shockwaves:

- Malign tumor
- Lung tissue
- Epiphyseal growth plate
- Large vessels and nerves

Blood thinning treatments are considered as a relative contraindication.

Conclusion

After 10 years of experience with this treatment it can be accepted as effective and safe if all the steps have been followed. It is an enormous improvement of the known trigger point therapy and offers new possibilities in the functional treatment of overload pathologies of the locomotor system. Once the diagnosis is established the treatment is easily applied and profits from patient's tolerance as it is non-invasive.

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Influence of Shock-Wave-Treatment on Migration, Proliferation and Genetic Expression of Fibroblasts

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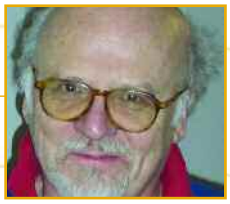

Introduction

The meaning of extracorporal shock wave thearapy (ESWT) for treatment of different skin lesions had increased during the last years. Starting with poor healing wounds which were treated with great success [1] several indications followed. Currently application of shock waves is for instance done in case of necrosis [2], burns [3] and wounds in veterinary medicine [4]. In all studies the fact that the treated area totally remodels to healthy and smooth skin of full integrity is common. This notice was also done in treatment of intact tissue, where tightness increased [5].

For these macro visual effects fibroblasts play a crucial role. They are one of the most important connective tissue cells of the dermis which is responsible for the elasticity and appearance of skin (**Figure1**). Fibroblasts produce the connective tissue fibers collagen, elastin and fibronectin. They are incorporated in the extracellular matrix mainly formed by hyaluronan. Hyaluronan contributes to tissue hydrodynamics what facilitates movement and proliferation of cells. Collagen and elastin are responsible for skin strength and elasticity, whereas fibronectin supports tissue repair either [6].

Examining the influence of shock-waves to proliferation, migration and genetic expression of fibroblasts in vitro may help to understand the underlying mechanism of ESWT.

Materials and Methods

Normal human dermal fibroblasts (NHDF) provided by PromoCell were cultivated in low serum medium (2%V/V). Treatment was carried out using the IVSWT Water Bath 2.0 [7], filled with degassed, thermostatically controlled water. During treatment culture flasks were filled with phosphate buffered saline of 37°C. Cells were treated using Orthowave 180c CP-155, MTS Europe GmbH and Piezoson 100plus, Richard Wolf GmbH. For Orthowave an energy flux density of 0,07mJ/mm2 or 0.15mJ/mm^2, frequency 5Hz, 300 pulses and device to cell distance 7cm was chosen. Cells treated by Piezoson 100plus were placed as near as possible to application membrane due to the small depth of penetration. Devices: FP4 (energy level 0,06mJ/mm^2) and IP20 (0,20mJ/mm^2) with 1000 pulses either.

For observing cell migration wound and heal assay was carried out. A cross was scratches into a confluent monolayer of cells growing in petri dishes. The closure of the wound was measured after 6, 12 and 24 hours. Based on fewer cells in wound and heal assay specified lower energy levels were used in that case.

Proliferation was measured 1 hour, day 3 and 5 after treatment carrying out cell counting with coulter counter, BCA protein assay and MTT assay.

Genetic expression of hyaluronan synthase (HAS2), collagen (COL1A2 and COL3A1), elastin (ELN) and fibronectin (FN1) was determined 6, 12, 24 hours as well as 3 and 5 days after treatment performing qRT-PCR. Housekeeping gene used was glyceraldehyde-3-phosphate dehydrogenase (**GAPDH**). Cells were cultivated in T12,5 for proliferation and T25 flasks for genetic expression measurements.

Results

Compared to non-treated cells migration is already visibly enhanced 6 hours after shock wave application. Over a period of 24 hours the wound of the treated cells is nearly closed whereas in the control cells it is still visible (**Figure2a and 2b**).

Cell Proliferation didn't show any difference between control and lower energy level treatment. Using higher levels cell viability decreased caused by treatment. Surviving cells showed slightly higher proliferation rate in cell counting than control group after 3 and 5 days. However MTT assay and BCA protein assay showed higher results for treated cells than cell counting. MTT increased especially straight after treatment, whereas the amount of protein rose after 3 days (**Figure3**). For shown data cells were scaled to 2,5x10^3 cells per flask after treatment.

Influence of energy nearly equals focusing gene expression. Little increase in collagen expression is seen within 24 hours. Positive change in elastin amount can be observed from 12 to 73 hours after treatment. Fibronectin and hyaluronan synthase remained at the control level during observation period of 24 hours. Afterwards especially hyaluronan synthase showed significant progression.

Discussion

Influence of ESWST on tissue influences many different pathways wherein the influence on fibroblasts may be just another brick in the wall. In vitro effects are not directly comparable to in vivo results what is especially shown in case of focused shock waves. Different devices were tried in this research. For treatment of adherent growing cells it is advantageous to use unfocused shock waves. Due to focused high energy cell detachment increases. Proliferation and migration cannot be determined in a satisfactory manner.

Currently using the IVSWT Water Bath 2.0 is the state of scientific knowledge for treating cells in culture. Nevertheless genetic expression is comparable to other devices. Acceptance of higher energy levels correlates with amount of treated cells for which reason migration had to be examined with lower levels.

The difference in MTT assay values compared to cell counting can imply a higher metabolic activity of treated cells especially after cell treatment what could be another reason for ESWT effects. It is well known that all influences of ESWT cannot be shown until a longer period than it's possible to cultivate cells without sub cultivating. This might be another limiting factor for in vitro research.

Acknowledgement

We thank Prof. Stephan Baldus for the possibility to work in his laboratories at the university hospital Hamburg-Eppendorf. Special thanks go to Dr. Anna Klinke and Dr. Denise Lau for their capable support.

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Figures:

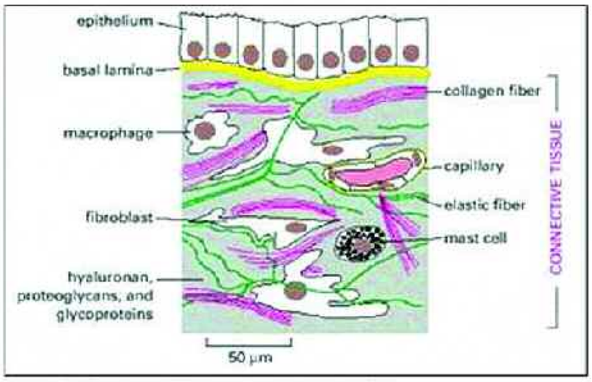

Figure 1: Connective tissue of human skin
Molecular Biology of the Cell. 4th edition. Alberts B, Johnson A, Lewis J, et al.

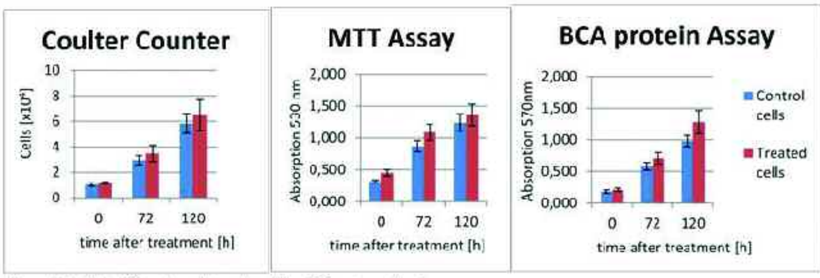

Figure 3: Cell Proliferation determined by different methods

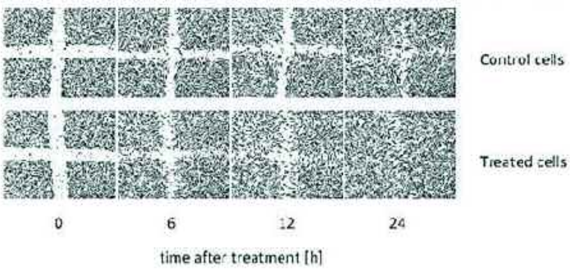

Figure 2a: Photographs of cell scratches according to time and treatment

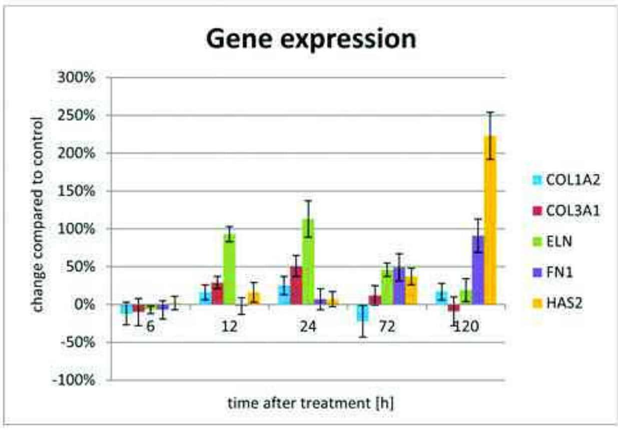

Figure 4: Gene expression - relative amount compared to control cells

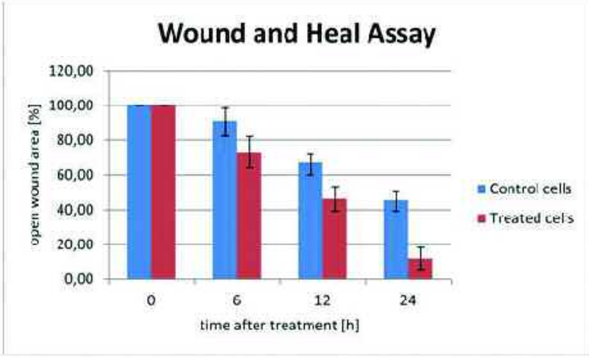

Figure 2b: Measured open wound area according to time and treatment

ESWT in Wound Care - Basic Research and Clinical Experience

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Abstract

Background: Non-healing wounds are a significant burden to both the healthcare system and the patient, often requiring protracted, intensive and quality-of-life-altering treatment. A novel approach to chronic wound management, extracorporeal shockwave therapy (ESWT) addresses the pathophysiological aspects of tissue ischemia and bioburden affecting chronic wounds.

Aim: To review the collective experimental and clinical data with ESWT from a translational research partnership (Austrian Cluster for Tissue Regeneration) and relevant published literature.

Methods: ESWT was applied in the context of animal and human studies: **1.** Rodent ischemic epigastric flap model (0.1mJ/mm^2, 0.10-0.30 pulses/cm^2 immediately and 24 hours before/after ischemic challenge); **2.** Patients with complicated, non-healing sub-acute and chronic wounds despite standard management, treated over 53-months in a prospective clinical study (100 pulses/cm^2, 0.1mJ/mm^2, initially bi-weekly then weekly in conjunction with wound debridement and moist dressings).

Results: Immediate and delayed post-surgical ESWT was associated with equally superior flap outcome (reduced planimetry-determined ischemic necrosis) compared to untreated controls. Tissue response to treatment was dose-dependent having maximum effect between 0.14 and 0.28 impulses/cm^2 at an energy level of 0.1mJ/mm^2. Induction of angiogenesis with up-regulation of the VEGF-R2 and increased quantitative tissue perfusion were found to play a pivotal role. Of 390 patients treated with ESWT, 72% demonstrated 100% wound epithelialization. Advanced patient age and wound size negatively impacted response to ESWT. There was no treatment-related toxicity.

Conclusions: Extracorporeal shock wave therapy has a protective, pro-angiogenic influence on experimental ischemic flaps, and has beneficial effects on wounds unresponsive to standard treatment.

Introduction

The incidence of patients suffering from chronic wounds is continuously rising worldwide and constitutes an extraordinary burden to patients' quality of life but also to health care expenses. The etiology is in the majority of cases multifaceted and treatment is often insufficient and limited to surgical intervention or special wound dressings [1-5]. Furthermore, treatment is disproportionally prolonged and often insufficient eventually resulting in therapy refractory wounds. Patient discomfort concomitant with immense health care expenses make these chronic wounds subject of intensive research. Alternative (effective) treatment options are highly desirable to reduce both cost expenses and patients discomfort.

Normally, uncomplicated soft tissue wound healing is a complex, well coordinated cascade of interdigitate processes on the cellular but also molecular level [2,3]. Ultimately, this physiological process leads to full tissue regeneration with complete restored tissue integrity and functionality. Hypoxia is known to be a strong inducer of a broad spectrum of mechanisms (adaptation of supply, metabolic and growth adaptation) facing tissue restoration [6,7]. However, depending on severity and duration, the diminished oxygen supply can also result in wound healing problems. This is aggravated especially in the elderly but also by co-morbidities such as diabetes and hypercholesterolemia. Studies have shown that in these cases the angiogenic response as a key event in the physiological wound healing process is remarkably reduced [8,9]. This leads to disturbed healing (chronic wounds, delayed healing wounds) but also patient psychological strain and extraordinary economical health care expenses.

Pathophysiologically, chronic wound conditions often result due to tissue ischemia/hypoxia which is well known to be one of the major factors complicating the normal wound healing process [10]. The surgical daily routine is regularly confronted with such compromised tissue perfusion. Once surgical treated, it often ends up in extensive operative revisions. In particular, this is seen in patients with co-morbidities such as diabetes and peripheral ischemic diseases (e.g. arteriosclerosis, peripheral arterial occlusive disease). The intrinsic capacity for physiological tissue regeneration is often severely impaired in these patients. If wounds require skin flap coverage in this patient population, then the transferred flaps may also be negatively affected by the underlying pathology. Skin flap surgery using autologous donor tissue is the treatment of choice for patients with large wounds or tissue defects [11]. Depending on the size of the defect, skin grafts, muscular flaps or composite flaps may be used. Necrosis of skin flaps, either partial or complete, remains a serious complication in skin flap surgery. Insufficient arterial (in-)flow with the accompanying decreased nutritional supply to hypoxic/ischemic tissues can be potentially overcome by therapeutic angiogenesis [12]. Numerous angiogenic factors have been studied for efficacy, for which an invasive approach with concomitant application of exogenous substances is common [13-15]. The mode of administration for angiogenic factors has also been studied, as the intended clinical use and efficacy are a concern when known adverse effects occur with systemic administration [16-18].

The therapy concept of chronic wounds (e.g. venous ulcers, diabetic ulcers, pressure sores) is up to now limited in both quantity and efficacy. Clinical standards include sufficient surgical and non-surgical (e.g. enzymatic) debridement with subsequent application of specialized dressings providing the wound with a moist environment [4,19]. However, several experimental approaches are currently evaluated to further improve chronic wound care. Studies show efficacy using gene therapy, recombinant growth factor application, bio-engineered skin (tissue engineering), and stem cell therapy [20-22]. However, these (experimental) treatment approaches target primarily only a single scope in the complex mechanism of pathological wound healing processes.

Shock waves were first clinically used in lithotripsy and are a potent means in disintegrating urinary stones hardly without side effects [23]. Since then, technique as well as application modes have been steadily modified and improved. In the last decades, shock wave application became attractive in the orthopedic and traumatic field treating (chronic) tendinopathies, pseudoarthrosis [24,25] but also chronic wounds [26,27]. Distinct advantages over other clinical but also experimental therapeutic approaches are the non-invasiveness and the avoidance of "exogenous medication" via various substances (e.g. growth factors, vasodilators). Although this encouraging proceedings, the biomolecular basis by which shock wave exerts its positive effects remains widely unclear. Few experimental studies suggest that vascular endothelial growth factor – a pivotal player in new vessel formation (angiogenesis) – is affected in terms of up-regulation [28,29]. Some studies also demonstrate the involvement of the nitric oxide system improving tissue perfusion [30,31].

In this work a brief overview of the experimental and clinical experiences using extracorporeal shock wave therapy in soft tissue wound care is provided. Own results in conjunction with recent publications in this field are discussed.

Basic Research

Background:

To better understand the (biomolecular) mechanism by which shock wave therapy influences and support impaired soft tissue wound healing, several investigators use ischemia models. Iatrogenic occlusion of blood flow (ischemia) constantly ends up in tissue necrosis accessible for various treatment modalities. One of the promising approaches in reducing/avoiding post-ischemic necrosis is "therapeutic angiogenesis" first mentioned by Hockel in 1993 [12]. The primary target is to stimulate local out-growth of vessels which are able to re-establish adequate perfusion. Several investigators hypothesized that induction of angiogenesis is also one of the key events in the biomechanisms of shock wave therapy.

Tissue Necrosis:

Effectiveness of ESWT in reducing ischemia-induced tissue necrosis was already shown experimentally in different rodent flap models [28,31-34]. In our laboratory, several flap models are established [35-38]. The rodent epigastric flap model (**Figure 1**) enables investigating ischemia induced necrosis and potential therapies along with perfusion measurements reflecting different degree of ischemia. In our opinion, it is a feasible model evaluating shock wave associated mechanisms and was used therefore in several ESWT studies. After short learning curve, surgery could be performed easily and flap outcome is highly reproducible.

After rendering a certain part of the flap ischemic (ligation and dissecting of an epigastric vascular bundle), 300 shock waves at 0.1 mJ/mm^2 were immediately applied to the ischemic challenged tissue. Attention was drawn that over the distal parts of the lungs (proximal flap) no direct perpendicular application was administered. Seven days after surgery and treatment, the area of necrosis was substantially reduced in comparison to the untreated control group assessed by a planimetric analyzing tool. This is in accordance with multiple other experimental studies using flap models and ESWT [31,32,34,39-41]. All of them showed a significantly reduced area of flap necrosis in the shock wave groups compared to non-treated controls. However, studies differed in the total amount of applied pulses (range: 500 – 2500 pulses) and the energy flux density (range: 0.09 – 0.15 mJ/mm^2). In addition, within these 6 studies, three different shock wave apparatus were used (one study missing apparatus specification). Our own investigations on dosage optimization showed that tissue response to treatment is dose dependent having maximum effects between 0.14 and 0.28 impulses/cm^2 at 0.1 mJ/mm^2 (manuscript in preparation). Although inhomogeneities between the studies (including our findings) exist, looking at the results on flap outcome a broad and safe treatment modality could be implied.

Influence of Treatment Time Point:

Even though this findings are of enormous clinical interest, clinicians (especially reconstructive trauma surgeons) are particularly confronted with delayed (e.g. 24 hours) tissue necrosis following reconstructive (flap) surgery. Thus, a treatment option to intervene in such cases with already macroscopically visible failure is highly desirable. ESWT fulfills this requirement as seen in delayed treatment (24 hours post ischemia) of the above mentioned rodent epigastric flap performed in our institution [42]. The 7 days follow-up showed that the ischemic challenged flap developed significantly less necrosis as compared with the untreated control group (**Figure 2**; manuscript accepted for publication in Annals of Surgery). In contrast to our study, where we single treated the flaps 24 hours post-ischemia Kuo et al. [34,43] applied shock waves twice (immediately after surgery and 1 day thereafter). Contrary to our significantly reduction of necrosis after delayed treatment, the flaps treated twice in the study of Kuo and colleagues showed also reduced but insignificant difference in areas of flap failure in comparison to controls. Possible explanations were given by the authors that additional treatment results in too high local energy density thus blocking blood perfusion and neovascularization. However, one of our clinical cases supports the thesis that ESWT might have the therapeutic potential to rescue established tissue necrosis (**Figure 3**) which we were also able to demonstrate experimentally.

A physiological process during wound healing is the wound contraction and reflects in some manner the quality of wound healing (e.g. collagen composition). Wound contraction should be minimal, especially for wound areas adjacent to joints which have to be covered by skin transplants or flap transfer. Preventing or minimizing contraction (extensive scar formation) results in less constrained range of motion in the involved joints and avoids surgical revisions. But also areas adjacent to orifices (face, beside the aesthetic point of view) are vulnerable to contraction and should be kept at a minimum. In the same study set-up, less flap contraction concomitant with less necrotic area was observed.

Encouraged by these findings, we addressed a further issue in elective treatment. Although in elective surgery a broad spectrum of possible complications can effectively be avoided, a residual risk which is incalculable exists especially in patients with co-morbidities (e.g. disturbed wound healing in diabetic patients). A tremendous amount of professional care efforts (wound care, wound revision) and social financial burden could be reduced if an elective treatment would be available to prepare the tissue as needed for the anticipated surgical intervention. Surgical procedures in a two stage manner were already evaluated to reduce necrosis and showed effectiveness [44]. For instance, in the first stage of flap surgery, only incisions will be made to induce the following increased tissue perfusion and to prepare the tissue for transfer in the second stage. Although this procedure shows a positive impact in the latter flap outcome, it nevertheless represents an invasive approach with its side effects (e.g. infection risk). When shock waves were applied experimentally to the flap prior to surgery, an equal reduction in necrotic flap area was found as compared to the above mentioned therapy groups (treatment immediately and 24 hours after surgery) where shock waves were applied delayed regarding ischemia. This is of great clinical relevance, because clinicians would have the opportunity to selectively treat patients prior to intended surgery who are at high risk of suffering from wound healing disturbances. A clinical study performed in 2008 [45] used this approach to treat surgical wounds after vein harvesting for coronary bypass grafts and had less wound complications in the shock wave treated group. However, treatment was performed after surgery being prophylactic but not really reflecting an elective intervention.

These findings in reducing tissue necrosis by ESWT are comparable with those studies which used exogenous growth factors (e.g. therapeutic angiogenesis) in the same indication [37,38]. An enormous advantage, however, over these studies is the non-invasiveness of our approach in the application of shock waves. Additionally, no adverse effects over the entire study period were observed. Further advantages are that the application is simple, it is well-received by the patients and is cost effective.

Influence of ESWT on Compromised Tissue Perfusion:

Probably one of the worst scenarios in reconstructive surgery (e.g. after free flap transfer with micro-anastomosis) represent tissue loss due to hypoxia or ischemia, as already mentioned above. Several different instruments and methods exist for early detection of this unfavorable condition. However, treatment options after verification of this status are scarce. In the described animal model, flap ischemia could be verified beyond doubt by clear blue demarcation 24 hours after vessel ligation. In addition, a clinically used, non-contact, Doppler based system could confirm the clinical macroscopic finding. The principle is that a low intensity laser light beam scans the surface of the skin and generates a 2-dimensional image of flap perfusion. With this technology the ischemic impact was confirmed in all test animals by a distinct reduction in flap perfusion.

In addition, using the Doppler based perfusion imaging system a clear enhancement of circulation in the experimental flaps was noticeable at the time point when shock waves were applied. Moreover, superficial tissue perfusion was maintained at a higher level during the entire study period (7 days) when compared to controls. This is confirmed by perfusion studies in a dorsal random flap model, which showed significantly increased blood flow following ischemic impact [34,46].

Two reasonable mechanisms could explain this finding. Nitric oxide (NO), a small ubiquitous molecule with vasoactive properties, causes vessel dilation which results in improved perfusion. Production and release is dependent on endogenous activity of its synthase. A study by Yan et al. [31] demonstrated a higher level of both nitric oxide and endothelial nitric oxide synthase (eNOS) in response to shock waves 8 hours after application. Oi et al. [30] confirmed eNOS up-regulation in an ischemic hindlimb model. Thus, this initial higher NO content stimulated by shock wave treatment could improve early perfusion and reduces early ischemia induced tissue damage.

Physiologically, angiogenesis takes place within 24 to 48 hours after impact. Vascular endothelial growth factor (VEGF) is the pivotal player in the angiogenic response, strongly induced by hypoxia. It is noteworthy that VEGF and NO influence each other [47]. Improved perfusion, initially accomplished by shock waves via NO as mentioned above, could then be maintained by shock wave induced angiogenesis. In fact, a number of studies showed up-regulation of VEGF [31,34,48-50]. Our own investigations in transgenic VEGF-R2 mice, revealed a distinct up-regulation of the main angiogenesis-related receptor VEGF-R2 due to ESWT, directly or indirectly through NO generation. Numerous histological and immunohistochemical analyses further showed enhanced levels of VEGF expression and higher content of capillaries. This improved circulation may have distinct benefits in wounds subjected to healing disturbances. All of this supports the hypothesis that angiogenesis with concomitant improved tissue perfusion/improved blood supply is one of the mechanisms of ESWT in ischemic/hypoxic wounds.

Furthermore, recent experimental studies demonstrate that ESW treated tissues, which were vulnerable to disturbed wound healing, show modified release kinetics of essential growth factors 51. Treatment resulted in increased cell proliferation, suppression of pro-inflammatory cytokines, and accelerated tissue regeneration and healing [52-54].

Transplant surgery is often confronted with limited healing of transferred tissue to the wound bed. Possible causes are seroma formation which prevents the nutritional supply from the wound bed to the overlying tissue, ultimately resulting in flap loss. Additionally, the lack of full tissue contact prevents the formation of new vessels (angiogenesis) which are mandatory for flap outcome, especially when subjected to a certain degree of hypoxia (ischemia). Macroscopic evaluation in our experiments showed that transplanted flaps treated with shock waves have better adherence to the wound bed in the ischemic challenged flap area in comparison to untreated controls. Surprisingly, this was not due to reduced seroma formation (nearly equal amounts between shock wave groups and control). Therefore, a strong induction of angiogenesis had to be induced by shock wave therapy originating primarily from the contralateral (perfused) side without necessitating the contact to recipient wound bed.

Clinical Experiences

Background:

Since the first clinical use of ESWT to disintegrate urinary stones decades ago [55], a series of clinical observations lead to expanded treatment indications. One of the first new fields of application was the treatment of non-union in bone fractures [24,25]. Nowadays extracorporeal shock wave therapy is used in the clinic to treat further different pathological conditions of the musculoskeletal system such as plantar fasciitis, (non-)calcifying tendinosis, and epicondylitis [56-58].

The serendipitous finding of chronic wound healing concomitant with the consolidation of non-union attracted the interest also to chronic wound conditions which are refractory to conventional therapy.

The Trauma Center Meidling is one of the largest trauma-clinics in Austria and Europe with around 70.000 trauma patients treated per year. More than 7.000 as indoor patients and more than 300 needing intensive care (166 beds / 8 ICU-beds).

The Trauma Center Meidling uses shock wave technology to treat non-union in bones already for 15 years. Furthermore, ESWT is used in delayed/non-healing or chronic wounds since 2004.

Patients and Etiology:

At regular intervals (initially biweekly, then weekly) patients are treated in our hospital primarily in an outpatient setting.

The etiologies of the treated soft tissue wounds are wide-ranging and include failure of primary wound closure after trauma and surgical intervention, disturbed wound healing after trauma, venous or arterial ulcers, pressure sores, and burns.

Those patients were enrolled who volunteered to participate in the study or refused standard therapy in order to avoid hospitalization. Exclusion criteria were as follows: pregnancy, patients with stage I (intact skin with signs of impending ulceration) and stage IV (full-thickness loss of skin and subcutaneous tissue and extension into muscle, bone, tendon, or joint capsule) decubitus ulcers (stage II and III decubital ulcers were included), superficial first degree, superficial second degree or circumferential burns requiring escharotomy, compartment syndrome, necrotizing fasciitis, or lymphedema. Patients with current participation in another clinical investigation of a medical device or a drug the requirements of which precluded involvement in the current study and those with active or previous (within 60 days prior to the study screening visit) systemic chemotherapy and/or radiation to the affected extremity to be treated by investigational shock wave therapy were excluded from this study. In addition, patients with physical or mental disability or geographical concerns (residence not within reasonable travel distance) that would hamper compliance with required study visits were also excluded. The study was approved by the Institutional Review Board of the AUVA Trauma Center Meidling.

Focused versus Unfocused/Defocused Shock Wave:

Shock wave devices based on the electro-hydraulic technology which are used routinely in various pathological musculoskeletal conditions consist of a under water spark plug with opposing electrodes. Shock waves generated by charging the opposing electrodes with maximum voltage concomitant with abrupt discharge are focused via a half ellipsoid shaped piece (reflector). Due to the geometric properties of this reflector all shock waves are reflected to an area (secondary focus – F2) at a defined distance away from the primary focal point (opposing electrodes – F1). Therefore, during treatment the exact alignment of the therapy head and the area to be treated (e.g. non-union = F2) is mandatory to gain maximum peak-positive acoustic pressure at this point.

Other than in lithotripsy or non-unions an unfocused or defocused shock wave in wound care indications is preferable due to the typically larger surface area of soft tissue wounds. To achieve such shock waves which are roughly plane to the treatment area the device which we use in our hospital has a parabolic instead of an ellipsoid reflector. Positioning the opposing electrodes at the primary focus F1 in a parabolic reflector will result in a planar wave which is emitted after the reflection of the primary spherical wave. The focal point (F2) of these plane waves is, by definition, "unfocused" or "defocused", which means that a secondary focal point F2 is found in the endless distance. Therefore the shock wave characteristics for the parabolic reflector could be defined as planar waves comprised of parallel rays of acoustic energy. The generalized parabolic reflector allows the plane waves to be bent slightly towards the central acoustical axis. Therefore the waves are unfocused, nearly parallel, and the energy density realized by this reflector configuration is higher than with an exact parabolic reflector and a large area is stimulated by the acoustical field.

Apparatus and Configuration:

Non-healing/chronic wounds are treated with unfocused extracorporeal shock waves. We used first the orthowave 180C (MTS Europe GmbH, Konstanz, Germany) to treat our patients. Since summer 2007 we use additionally the ActiVitor (SwiTech Medical AG, Switzerland) in the same clinical set-up (**Figure 4**). Considering previous experience treating various musculoskeletal disorders such as tendinopathies we concluded to apply an average energy flux density of 0.1 mJ/mm^2 typically applied for these indications in the range of 0.03 – 0.15

mJ/mm^2. Experimental dose-response studies indicated 100 pulses per cm^2 as the optimal dose for the proposed indication. Following configurations of ESWT were applied to each individual:

Orthowave 180C: 100 total impulses per squarecentimetre at an energy flux intensity of 0.1 mJ/mm^2 (level 5), frequency of 5 pulses/sec.

ActiVitor: Equivalent parameters in terms of impulses/cm^2, energy flux intensity and frequency were used.

Treatment Modalities and Additional Wound Care:

We treat our patients (bi-)weekly primarily in an outpatient setting. At presentation and on each other evaluation time points wounds are clinically described concerning wound area, wound depth, wound cavitations, signs of inflammation, and exudation state. Additionally, digital images are taken for documentation. If necessary, wounds are debrided prior to shock wave treatment to remove avital/necrotic tissue as it will be also performed in the daily clinical routine.

Until yet, no anesthesia was necessary in any of the patients enrolled, as the delivered shock wave was defocused and therefore not causing relevant pain.

After adequate preconditioning of the wounds sterile ultrasound gel was applied on the wound surface as well as on adjacent tissue. Then, parameters of the shock wave device were adapted to each individual treatment. Shock waves were administered directly on the wounds but also on the surrounding tissue. Post treatment the gel was removed and special wound dressings (standard or advanced) were applied according to wound needs. Between the treatment sessions patients received advanced wound dressings according to wound needs. All pre-treatment data including digital photography were continuously updated during each single-time session.

Collected/Evaluated Parameters and Study Readout:

Patient variables analyzed included age at presentation and gender. Anatomic sites were classified as soft tissue wound of the upper and lower extremity, trunk or head. Wound-specific variables included etiology (disturbed healing, post-traumatic necrosis, venous stasis ulcer, decubital stage II/III ulcer, plaster cast pressure ulcer, arterial insufficiency ulcer, or second or third degree burn), wound size in cm^2, wound depth (superficial or deep), and wound cavitations (none, ≤ 1cm, or > 1 cm). Shock wave therapy related factors analyzed were number of shock wave treatments and shock wave pulses delivered. In addition, in wounds responsive to ESWT the mean time from first treatment to complete healing was assessed.

Primary study endpoint was to evaluate the feasibility of shock wave treatment in sub-acute/chronic wounds of various etiologies failing standard wound care. Secondly, the overall healing rate in response to treatment was evaluated and referred to different variables such as patients' age, wound etiology, and wound size. Treatment parameters were assessed also with respect to the healing rate.

Definitions:

Wounds of the head were those located on at or above the skull base or involving the face.

Wounds lower the groin were defined as lower extremity wounds. Wounds lower the shoulder were categorized as upper extremity wounds. Wounds of the superficial trunk including the gluteal and sacral regions were defined as truncal.

Disturbed healing was defined as partial or complete failure to heal after primary closure of a

surgical wound. Skin grafts or flaps were not included in this study. Soft tissue wounds resulting from direct penetrating or blunt trauma associated with necrosis of epithelial and non-epithelial extra-skeletal structures (e.g. fibrous and adipose tissue, skeletal muscle, vasculature, etc.) were categorized as posttraumatic.

Venous stasis ulcers were non-healing sores or wounds of the lower leg near the medial malleolous in patients with known dysfunction of the perforating draining veins of the leg apparent by duplex ultrasound. These were typically characterized by a shallow, exuding ulcer with diffuse edges, brown pigmentation, surrounding skin scaling and generalized edema of the affected extremity.

Decubitus ulcers were defined as sores resulting from pressure exerted on the skin, soft tissue, muscle and bone by the weight of the patient against a surface beneath them. For the purpose of this trial, decubitus ulcers demonstrating partial-thickness loss of skin involving epidermis and dermis as well as decubitus ulcers showing full-thickness loss of skin with extension into subcutaneous tissue, but not through the underlying fascia were included. Pressure sores in this study characterized by partial thickness loss of skin involving epidermis, dermis and/or subcutaneous tissue, but not superficial investing muscular fascia, resulting from skin necrosis attributable to localized pressure from the inner aspect of a plaster cast over a bony prominence were defined as plaster cast pressure ulcers. An arterial insufficiency ulcer was defined by chronic, non-healing, distal limb ulceration in patients with known atherosclerotic peripheral vascular disease unable to receive revascularization due to medical co-morbidity or lack of suitable outflow artery in the affected extremity.

These ulcers were typically deep with localized edema and shiny, hairless surrounding skin. Burn wounds in this study were defined as non-circumferential deep second or third degree burns typically characterized by presence of blisters, mottled/patchy appearance and diminished or no sensation.

Wound depth was defined relative to the dermis. Soft tissue wounds extending beyond the dermis into the underlying subcutaneous tissue were defined as deep. Those wounds confined to the epidermis and dermis were regarded as superficial. Wound cavity or soft tissue defect was defined as absent, ≤ 1cm, or > 1 cm relative to the epidermis. Wound duration was defined from the date of diagnosis of the soft tissue wound under study to the date of first shock wave application. No patients received antibiotic therapy during shock wave treatment.

Results and Discussion:

Study Summary:

During August 2004 and December 2008 (= 53 months), patients with sub-acute and chronic wound conditions were enrolled as part of clinical routine. They underwent treatment with unfocused shock wave therapy in this prospective non-randomized single armed study. Parts of this open study with 208 patients were published in 2007 by Schaden et al. [26].

During the 53 months, 390 patients were included (summary of patient, wound, and treatment related factors in **Table 1**) for shock wave treatment. The mean age of the patient cohort was 59.4 years ranging from 11 to 102 years (median: 60 years). It is notable that of these 390 patients 57.4% were male and 42.6% were female. This gender distribution could be due to our trauma centers´ prevalence of treating working accidents. Comparing age and gender the mean age in the males was 60.8 ranging from 11 to 102 years (median: 50) while the age of females was in mean 57.6 within 20 and 97 years (median: 76).

Most common comorbidies were diabetes mellitus type II, and vascular hypertension which is typically associated with chronic or delayed/non-healing wounds ("diabetic foot ulcer"). A large number of patients reported smoking behavior which also negatively influences wound healing [59,60]. Therefore it is more interesting, whether diabetes mellitus type II nor smoking affected adversely treatment outcome although patients concerned maintained smoking during therapy duration.

The most common location of wounds treated was the lower extremity (79.7%) followed by the upper extremity (14.9%). Residual wounds were distributed to the trunk and the head. Most frequently observed wound etiology in this cohort were wound healing disturbances of primary acute (direct penetrating or blunt trauma) wounds (43.3% = 169 patients). Posttraumatic necrosis (epithelial and non-epithelial extraskeletal structures) was found in 31.3% (122 patients) of the patients representing the second main wound etiology. Treatment of the various ulcers was performed in 83 patients. Delayed/non-healing burn wounds were treated in 16 patients.

The mean wound size independent of wound etiology was 11.6 cm^2 ranging from 0.24 to 375 cm^2 (median: 5cm^2). Looking at the different types of wounds it was found that posttraumatic tissue necrosis had the largest wound surface area before ESWT with a mean size of 12.6cm^2 (range: 0.24 – 140cm^2, median: 6cm^2) followed by decubital ulcers (mean: 12.2cm^2, range: 0.5 – 120cm^2, median: 6cm^2) and wounds with healing disturbances (mean: 12.2cm^2, range: 0.3 – 375cm^2, median: 4cm^2). Most of the wounds were superficial meaning that they did not exceed beyond the dermis (276 wounds out of 390). Plaster cast pressure ulcers showed in 54.6% a wound depth which extended the dermis layer and reached the subcutaneous tissue. In the decubital ulcers this was the case in 40%, in 37.7% in the disturbed healing wounds and in 33.3% in arterial ulcers. 33.5% of all included ulcers were judged as deep ulcers. Wound cavities were present in 60 patients (=15.4%) while in 68.3% the cavity was smaller than 1cm and in residual 31.7% the cavity showed an extension of or greater than 1cm.

Treatment Outcome:

Of the 390 patients treated with ESWT during August 2004 and December 2008, of which 330 patients could be evaluated, 279 patients showed complete healing of their wounds (=71.5%) while 5.4% were non-responsive to shock wave therapy and wound size remained unchanged when compared to the beginning of therapy. In total 60 patients (15.4%) missed the follow-up without having information whether wounds were healed or stayed unchanged. At the end of therapy 3.3% (13 patients) had a greater than 50% healing response in comparison to baseline wound size and 4.4% (17 patients) smaller than 50% (for summary of treatment outcome see **Table 2**).

The mean time from the first treatment with ESW to complete healing was 44 ± 44 days (mean ± SD; median: 33.5 days, range: 4 – 381 days). Wounds with healing disturbances as well as burn wounds showed the fastest healing with a median duration from the first treatment to complete healing of 29 and 28 days, respectively (range: 4 – 134 days and 7 – 62 days, respectively). In the ESWT responsive decubital ulcers and venous stasis ulcers it took longest to heal (median: 63 days (range from 14 – 224 days) and median: 61 days (range from 7 – 237 days).

Analyzing the influence of the wound etiology and healing rate when delayed/non-healing burn wounds show the best efficacy of ESWT with a healing rate of 94% followed by post-traumatic wound necrosis with a treatment success of 83%. Descending success has been found in wound healing disturbances (74%), plaster cast pressure ulcers (73%), arterial insufficiency ulcers (67%), and decubital ulcers (65%). However, all of the mentioned show a better healing rate than 50% following shock wave therapy. Contrary, the worst results showed the venous stasis ulcers with a success rate of only 28%.

A clinical study evaluating ulcers primarily of the lower extremity treated with ESWT showed a healing rate of 36% in venous stasis ulcers which is comparable to our results. In contrast, 69% of post-traumatic ulcers which were also investigated healed completely after shock wave therapy [61].

No differences exist between both genders. On the other hand, patients' age is related to wound outcome independent of wound etiology. In general, higher age is associated with a higher incidence of failure to complete healing after ESWT (**Figure 5**).

The wound size also influences the healing rate independently of wound etiology, except for the plaster cast pressure ulcer where no correlation between wound size and outcome could be found (**Figure 6**). However, not surprisingly, larger wound size comes along with worser outcome. In the study of Schaden et al. in which a multivariant logistic regression analysis was performed, patient age, and wound size emerged as independent predictors of complete healing [26].

The wound depth also plays a role in the healing tendency in response to ESWT although the influence of this parameter is not as important as primarily thought. While superficial wounds completely healed in 73% of the cases this was only in 67% for deeper wounds reaching the subcutaneous layer. If wound cavities are pre-existent the healing rate after shock wave therapy is slightly lower (67%) than in wounds without any cavities (72%). Hereby it is notably that no differences were found if the cavity is larger or smaller than 1cm. This is in accordance to the analyses of Schaden et al. [26].

In average wounds were treated 2.9 times (range from 1 – 15) whereby wounds receiving 14 and 15 sessions were performed in only 1 case, each, and 11 to 13 treatment session were never necessary. As expected, venous stasis ulcers had to be treated more often (mean: 5.2 times) with a median of 1700 pulses (range: 150 – 44700 pulses). A huge number of patients only needed 1 session. The mean total amount of pulses applied was 1482.7 (range from 100 to 44700).

Shock wave treatment is characterized by number of pulses applied, the frequency and energy flux density. Until now, we normally use the same energy level as well as frequency due to empirical experimental but also clinical data and to keep the treatment variables low.

Only the total number of shock wave pulses differs and is adopted to wound surface area (approximately 100 pulses/cm^2). However, changing the other parameters it is likely that also outcome is influenced. Therefore, several studies are performed (see above – basic research) investigating this topic.

Since 2007 we use additional the ActiVitor (SwiTech Medical AG, Switzerland) in parallel to the orthowave 180C (MTS Europe GmbH, Konstanz, Germany). In comparing this two systems (both use electrohydraulic mode) no differences could be observed in terms of treatment efficacy, although these findings only reflect the clinical observations and no comparative study was carried out.

Adverse Events:

There were no reported cardiac, neurological, dermal, thermal or allergic reactions or adverse events. For the few patients that reported pain during unfocused shock wave treatment appropriate reduction in energy flux density (0.06-0.08 mJ/mm^2) and frequency (2 – 3 pulses per second) for the first 50 to 100 impulses with subsequent gradual escalation to target parameters was well tolerated. However, no patient needed further local or general anesthesia. During treatments no event of bleeding, petechiae, hematoma or seroma formation was observed. All ESWT was administered on an outpatient basis (excluding those patients hospitalized for various medical reasons). No clinically evident wound infection developed in soft tissue defects treated with shock waves, and no patient in this study experienced any deterioration of the treated wound.

Conclusions

In summary ESWT was found as a feasible therapeutic tool in preventing experimental necrosis in ischemic challenged tissue. The therapeutic effect was seen independent of time of treatment. This is of important clinical relevance, because it provides clinicians with a certain therapeutic window in which ESWT is effective. Tissue subjected to hypoxia/ischemia after surgery is suitable for this non-invasive, cost-effective approach and may help to reduce extensive surgical revisions and prolonged wound care. Likewise, patients susceptible to wound healing disturbances could be treated prior to necessary surgical interventions, thus minimizing postoperative complications.

The experimental findings support the clinical results of ESWT in patients suffering from delayed/non-healing or chronic wounds. Multiple indications in the field of soft tissue wound healing are highly responsive to ESWT, except venous stasis ulcers which show limited success.

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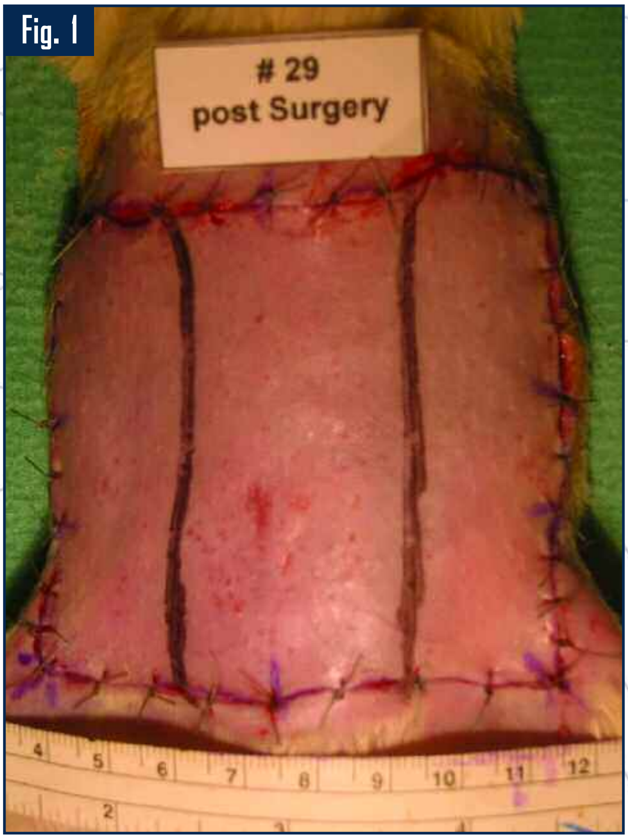
Fig. 1



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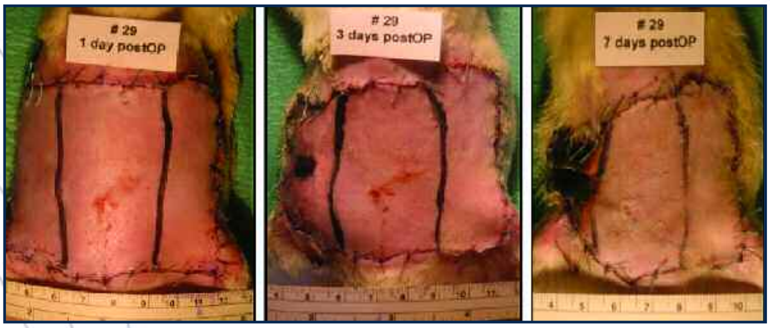


Fig. 2

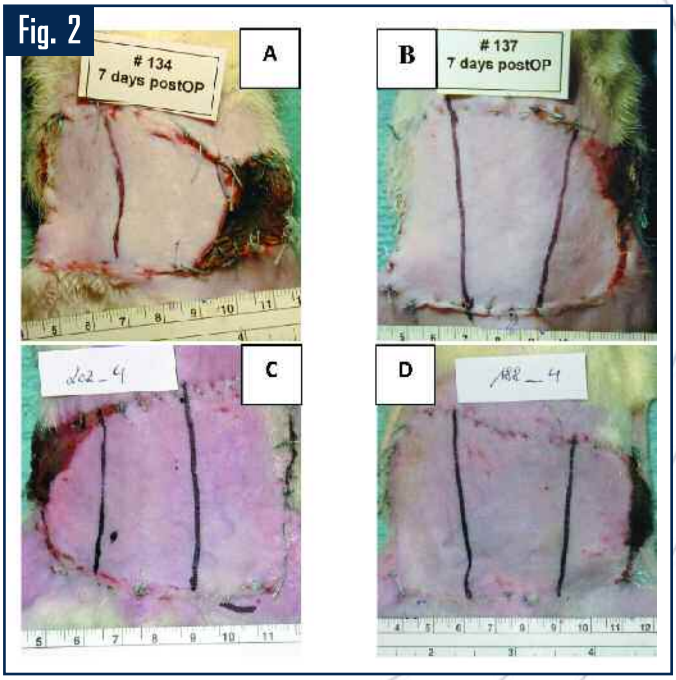


Fig. 3

Fig. 4

Fig. 5

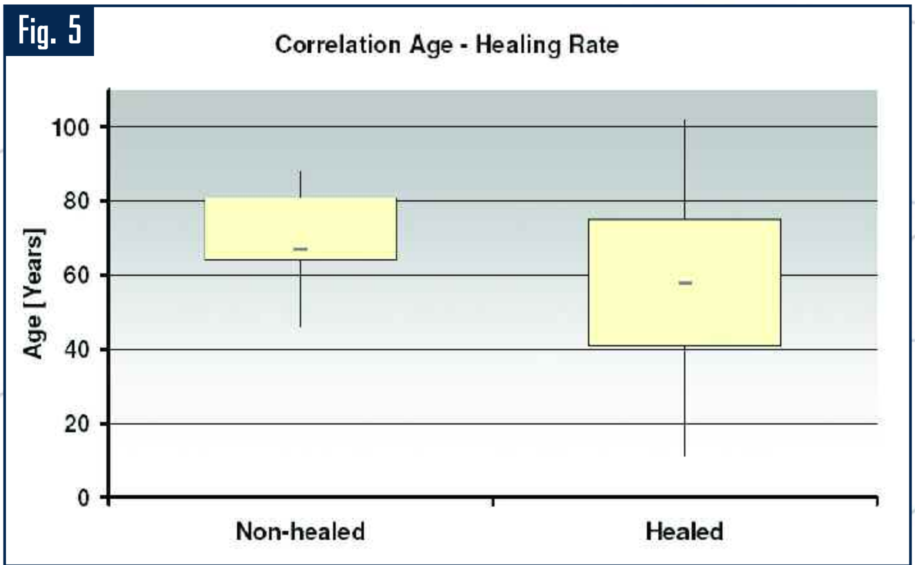
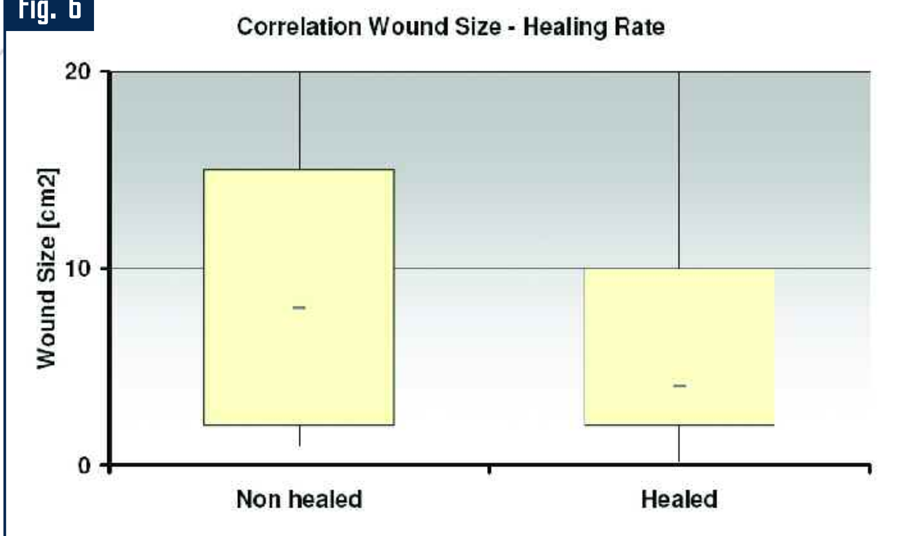


Fig. 6



Tables:

Table 1.

Patient Characteristics I

Parameter	*No. of patients*	*Percentage (%)*
Total number of study subjects	390	100
Gender		
- Female	166	42.6
- Male	224	57.4
Age		
- Mean	59.4	
- Median (range)	60 (11-102)	
Wound site		
- Upper extremity	58	14.9
- Lower extremity	311	79.7
- Trunk	18	4.6
- Head	3	0.8
Wound Etiology		
- Disturbed wound healing	168	43.1
- Post-traumatic wound necrosis	122	31.3
- Venous stasis ulcer	43	11.0
- Decubitus ulcer	20	5.1
- Plaster cast pressure ulcer	11	2.8
- Arterial insufficiency ulcer	9	2.3
- Burn wound	16	4.1

Table 2.

Patient Characteristics II

Parameters	Disturbed wound healing n = 169 No.	%	Post-traumatic necrosis n = 122 No.	%	Venous stasis ulcer n = 43 No.	%	Decubitus ulcer n = 20 No.	%	Plaster cast pressure ulcer n = 11 No.	%	Arterial insufficiency ulcer n = 9 No.	%	Burn wound n = 16 No.	%	Total patients No.	%
Wound Location																
Head	2	1	0	0	0	0	1	5	0	0	0	0	0	0	3	0.8
Trunk	7	4	1	1	0	0	8	40	0	0	0	0	2	12	18	4.6
Upper Extremity	28	17	17	14	0	0	1	5	4	36	0	0	8	50	58	14.9
Lower Extremity	132	78	104	85	43	100	10	50	7	64	9	1	6	38	311	79.7
Wound Size (median, range)																
< 10 cm2	125	74	80	66	31	72	16	80	9	82	8	89	9	56	278	71.3
> 10 cm2	44	26	42	34	12	28	4	20	2	18	1	11	7	44	112	28.7
median (range), cm2	4 (0.3 - 375)		6 (0.2 - 141)		4 (1 - 50)		6 (0.5 - 120)		2 (0.5 - 18)		4 (1 - 45)		9,5 (1 - 36)		5 (0.2 - 375)	
Superficial Wounds	107	63	96	79	33	77	12	60	5	45	6	67	16	100	275	70.5
Deep Wounds	62	37	26	21	10	23	8	40	6	55	3	33	0	0	115	29.5
Wound Cavitation																
None	137	81	108	89	37	86	14	70	10	91	8	89	16	100	330	84.6
< 1 cm	22	13	9	7	6	14	3	15	1	1	0	0	0	0	41	10.5
> 1 cm	10	6	5	4	0	0	3	15	0	0	1	11	0	0	19	4.9
Complete Healing	124	73	101	83	12	28	13	65	8	73	6	67	15	94	279	71.5
No. ESWT Tm. *	2 (1 - 8)		2 (1 - 9)		4 (1 - 14)		2 (1 - 10)		2 (1 - 3)		2 (2 - 6)		2 (1 - 4)		2 (1 - 14)	
No. ESWT Pulses *	700 (100 - 7300)		700 (100 - 6000)		925 (300 - 5500)		600 (200 - 6350)		500 (200 - 1460)		1300 (800 - 2100		800 (150 - 3000)		700 (100 - 7300)	
Time of Healing, d *	29 (4 - 134)		31 (6 - 381)		61 (7 - 237)		63 (14 - 224)		30 (7 - 105)		41 (13 - 126)		28 (7 - 237)		34 (4 - 381)	

* median (range) in completely healed wounds; Tm ... Treatments

% refers to percent od column total

Instructions for Authors

Newsletter of Extracorporeal Shockwave Therapy is an international, peer-reviewed journal produced by International Society for Musculoskeletal Shockwave Therapy(ISMST) and is issued three times a year

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Scientific research:

Theoretical or experimental (basic or applied) scientific research or the practical application of this research. The article should consist of an abstract, key words, introduction, methods, results, discussion, and conclusion.

Length: The manuscript should be no longer than 2,500 words, including title page, abstract, references, legends and tables.

Review articles:

Review articles on topics of general interest are welcomed. Reviews should include the specific question or issue that is addressed and its importance for the shockwave therapy community, and provide an evidence-based, balanced review on this topic. The article should include a description of how the relevant evidence was identified, assessed for quality, and selected for inclusion; synthesis of the available evidence such that the best-quality evidence should receive the greatest emphasis; and discussion of controversial aspects and unresolved issues. Meta-analyses also will be considered as reviews. Authors interested in submitting a review manuscript should contact the editorial office prior to manuscript preparation and submission.

Length: Approximately 2,000 to 2,500 words and no more than 40 references.

Case reports

Authors are encouraged to submit articles with interesting case reports with relevant information regarding diagnosis and therapy, unique for shockwave therapy. The articles should be short, accurate and easy to understand, and should consist of the following:

- A summary with the clinical relevance;
- An introduction explaining the clinical problem;
- A short report of the cases, consisting of history, physical examination, further investigation, treatment and follow-up.
- A discussion, whereby the clinical consequences are described and the most interesting aspects of the case report.

Length: Approximately 750 to 1,200 words and a maximum of 15 references.

Clinical lesson

Authors are invited to give a description and background information of developments in the field of further diagnostics and clinical tests and methods that are relevant to all aspects of shockwave therapy, training and rehabilitation. It is not necessary to include examples of patients, as in case reports. The articles should be up-to-date, short, accurate, and easy to understand and should contain the following:

- A summary with the clinical relevance (max. 150 words)
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- A conclusion with the practical relevance and practical tips.

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National organisation communications

National organisations are invited to describe any aspect of medical care or science in their country, e.g. the function of their medical committee, medical care of their players, research that is being conducted etc.

Approximately 300 to 500 words

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Letters discussing an article that has been published in Journal of Extracorporeal Shockwave Therapy have the greatest chance of acceptance if they are sent in with 2 months of publication. Letters that are approved will be forwarded to the author, who will have 6 weeks to respond. The original letter and the reply will be published simultaneously.

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Authors are invited to submit summaries of published article of particular interest for the shockwave therapy community. The opinion of the author should be stated following each summary.

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Authors are invited to submit reports of conferences they have attended, and to include one to three photographs taken at the meetings. Please include the names and highest titles of the persons that can be identified in the photographs. Summaries of work presented at the conference may be submitted for publication as well.

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- On the title page include the full names, highest academic degrees, and affiliations of all authors. If an author's affiliation has changed since the work was done, list the new affiliation as well.
- Figures, summary tables and diagrams should be numbered consecutively throughout the paper. Photographs should be clearly labelled.
- **References**. Number references in the order they appear in the text; do not alphabetise. In text, tables, and legends, identify references with superscript Arabic numerals. When listing references, follow AMA style and abbreviate names of journals according to Index Medicus. List all authors and/or editors up to 6; if more than 6, list the first 3 followed by et al.

– **Journal:** Kibler WB. The role of the scapula in athletic shoulder function. Am J Sports Med. 1998;26(2):325-337.

– **Book:** Perry J. Biomechanics of the shoulder. In: Rowe CR, ed. The shoulder. London: Churchill Livingstone, 1988:1-15.

- Footnotes should be avoided.

Review process

Contributions will be reviewed by the editorial board for scientific research, review papers, case reports, clinical lessons, and abstracts. Manuscripts should meet the following criteria: material is original; writing is clear; study methods are appropriate; the data are valid; conclusions are reasonable and supported by the data; information is important; and topic has general shockwave therapy interest.

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