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MTS Science Horizon Scan 1st Half-Year 2020

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Austrian Cluster for Tissue Regeneration, Vienna, Austria.

Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, AUVA Trauma Research Center, Vienna, Austria.

Gollmann-Tepeköylü et al., 2019: **miR-19a-3p containing exosomes improve function of ischemic myocardium upon shock wave therapy.**

Cardiovasc Res. 2019 Aug 13. pii: cvz209. doi: 10.1093/cvr/cvz209. [Epub ahead of print]

Aims: As many current approaches for heart regeneration exert unfavourable side effects, the induction of endogenous repair mechanisms in ischaemic heart disease is of particular interest. Recently, exosomes carrying angiogenic miRNAs have been described to improve heart function. However, it remains challenging to stimulate specific release of reparative exosomes in ischaemic myocardium. In the present study, we sought to test the hypothesis that the physical stimulus of shock wave therapy (SWT) causes the release of exosomes. We aimed to substantiate the pro-angiogenic impact of the released factors, to identify the nature of their cargo, and to test their efficacy in vivo supporting regeneration and recovery after myocardial ischaemia.

Methods and results: Mechanical stimulation of ischaemic muscle via SWT caused extracellular vesicle (EV) release from endothelial cells both in vitro and in vivo. Characterization of EVs via electron microscopy, nanoparticle tracking analysis and flow cytometry revealed specific exosome morphology and size with the presence of exosome markers CD9, CD81, and CD63. Exosomes exhibited angiogenic properties activating protein kinase b (Akt) and extracellular-signal regulated kinase (ERK) resulting in enhanced endothelial tube formation and proliferation. A miRNA array and transcriptome analysis via next-generation sequencing were performed to specify exosome content. miR-19a-3p was identified as responsible cargo, antimir-19a-3p antagonized angiogenic exosome effects. Exosomes and target miRNA were injected intramyocardially in mice after left anterior descending artery ligation. Exosomes resulted in improved vascularization, decreased myocardial fibrosis, and increased left ventricular ejection fraction as shown by transthoracic echocardiography.

Conclusion: The mechanical stimulus of SWT causes release of angiogenic exosomes. miR-19a-3p is the vesicular cargo responsible for the observed effects. Released exosomes induce angiogenesis, decrease myocardial fibrosis, and improve left ventricular function after myocardial ischaemia. Exosome release via SWT could develop an innovative approach for the regeneration of ischaemic myocardium.

Clinical relevance: Milestone research for working mechanism and future applications. MTS device: Orthogold180, CG050-P

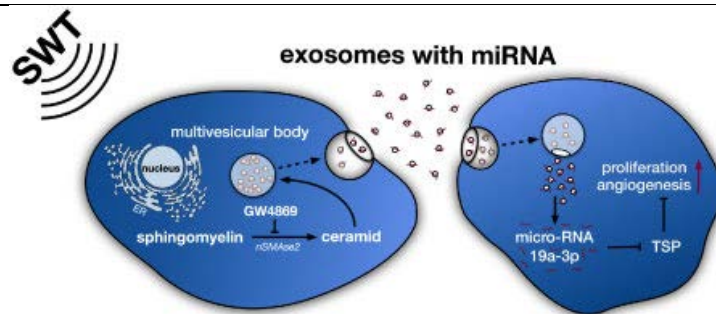


Figure 6 Suggested mechanism of SWT-induced angiogenic effects. SWT stimulates nSMase2-catalysed and GW4869-sensitive formation of ceramide, the accumulation of which is known to trigger budding of exosomes into MVBs.³⁵ Upon fusion with the cell membrane, these MVBs release exosomes into the extracellular space which are then taken up at the surface of receiving cells, either by fusion with the target membrane or by endocytosis.³⁶ The exosomes can then release their cargo, part of which is miR-19a-3p. The latter can act as an inhibitor of TSP-1,³¹ a known suppressor of angiogenesis and proliferation, which in effect causes a net stimulation of these processes.

Paracelsus Medizinische Privatuniversität Diplomstudium Humanmedizin.
Unfallklinik Salzburg Unfallchirurgie und Orthopädie.

Fallnhauser et al., 2019

Handchir Mikrochir Plast Chir. 2019 Jun;51(3):164-170. doi: 10.1055/a-0914-2963. Epub 2019 Jun 5.

[Extracorporeal Shockwave Therapy for the treatment of scaphoid delayed union and nonunion: a retrospective analysis examining the rate of consolidation and further outcome variables].


German

BACKGROUND:

Operative procedures are considered gold standard in the treatment of scaphoid nonunion, albeit their considerable complexity and the risk of intraoperative complications. High energy extracorporeal shockwave therapy (ESWT) offers a non-invasive treatment option for scaphoid nonunion. The aim of this study was to explore the rate of bony consolidation and further outcome variables in patients with delayed union of scaphoid fractures and scaphoid nonunion treated with ESWT.

PATIENTS AND METHODS:

Due to delayed union (21) or nonunion (21) of a scaphoid fracture 42 patients (37 men, and 5 women) with an average age of 48,3 (15-66) years underwent ESWT followed by immobilization in a forearm cast including the proximal phalanx of the thumb for 6 to 8 weeks. In 13 patients the fracture was initially treated, 8 with immobilization, 5 with screw fixation. In 5 of the 29 patients without an initially treatment, the fracture resp. nonunion was secondarily treated with screw fixation (2) or a medial femur condyle (3) but failed to heal. 10 to 12 weeks after the ESWT bony healing was controlled with computed scanning in the long axis of the scaphoid. If 50 % of diameter of the scaphoid showed trabecula bony healing was considered. Factors with potential influence on bony healing (site of the fracture/nonunion, scapholunate angle, patient's age, Body Mass Index, smoking and alcohol consume) were analyzed. In addition, 34 patients underwent a clinical follow-up examination including DASH and Mayo Wrist Score, pain analyzes (VAS).

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RESULTS:

Seventy-one per cent of patients showed scaphoid fracture consolidation using ESWT. In 7 out of 8 patients with conservative treatment and in 4 out of 5 patients with screw fixation of the initial fracture bony healing was achieved. From the 5 patients with secondary surgical treatment of the scaphoid only 1 patient, treated with a medial femur condyle, failed to heal the scaphoid. 15 out of the 24 initially non-treated scaphoid fractures healed. The time between ESWT and the documented bony healing averaged 8.4 months (256 days). Neither fracture site, nor the scapholunate angle, alcohol and tobacco use, as well as biometric factors, such as age and BMI had influence on the success rate of the ESWT. Side effects of the ESWT were limited to local skin irritations and petechial bleedings.

CONCLUSION:

ESWT has a positive effect regarding bony healing of scaphoid fracture with delayed fracture healing and nonunion with a success rate of 71 %. The complication rate is low, and the clinical results regarding wrist motion and pain are satisfying. Further investigations are necessary to evaluate the input of fracture/nonunion characteristics like the morphological appearance on bony healing.

Clinical relevance: delayed unions, non-unions are very important indications for the trauma clinics. Study did confirm the good treatment outcome of Orthogold280

Department of Oral and Maxillofacial Surgery, Bafra Oral and Dental Health Hospital.
Department of Histology and Embryology, Faculty of Medicine, Ondokuz Mayıs University,
Samsun, Turkey.


Özkan et al., 2019:

J Craniofac Surg. 2019 Jun;30(4):1298-1302. doi: 10.1097/SCS.0000000000005213.

Effect of Electrohydraulic Extracorporeal Shockwave Therapy on the Repair of Bone Defects Grafted With Particulate Allografts.

Abstract

This study determined the effect of electrohydraulic extracorporeal shockwave therapy (ESWT) on the healing of mandible defects repaired using particulate allogenic bone grafts. This study included 20 male Wistar rats aged 12 weeks. In all the animals, a critical-sized defect of 4-mm diameter was created in the mandible and the defect area was filled with particulate allograft. Next, the rats were divided into 2 groups, allograft (G) (n=10) and allograft+ESWT (GE) (n=10). On days 3, 5, and 7 after the grafting, rats in the GE group received ESWT involving 200 pulses with an energy flux density of 0.19 mJ/mm. Five rats in each group were sacrificed at the end of week 4 and at the end of week 8. Defect areas were examined radiologically by performing high-resolution computed tomography and stereologically by using the Cavalieri method. Obtained data were compared by performing statistical analysis. Radiological evaluation showed that bone density was higher in rats in the G group than in those in the GE group at week 4. In contrast, bone density was higher in rats in the GE group than in those in the G group at week 8. Stereological examination showed that new bone, connective tissue, and capillary volumes were higher in rats in the GE group than in those in the G group at both weeks 4 and 8. The authors' results indicate

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that **repeated doses of ESWT accelerate the healing of bone defects repaired using allogenic bone grafts.**

Clinical relevance: Animal study. Bone regeneration – positive outcome for MTS device: orthogold100, applicator OP155

Department of Oral and Maxillofacial Surgery, Rambam Medical Care Center, Haifa, Israel, Israel; and Ruth & Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel.

Ginini et al., 2018:

J Oral Maxillofac Surg. 2019 Mar;77(3):629-638. doi: 10.1016/j.joms.2018.07.018. Epub 2018 Jul 24.

Effects of Timing of Extracorporeal Shock Wave Therapy on Mandibular Distraction Osteogenesis: An Experimental Study in a Rat Model.

Distraction osteogenesis (DO) is an established method for bone lengthening in the craniofacial skeleton. Its major drawback is the long consolidation period with attendant morbidity and possible complications. Several methods have been suggested to shorten the consolidation period. We evaluated the timing and effects of extracorporeal shock wave therapy (ESWT) on bone mineralization and extracellular bone matrix proteins during mandibular DO.

MATERIALS AND METHODS:

Twenty-seven rats underwent mandibular DO (latency period, 3 days; distraction period, 10 days; 0.5 mm/day) and were divided into 3 groups according to the timing of ESWT application: group I (control) received no treatment, whereas groups II and III received ESWT (0.18 mJ/mm²) before and after the active distraction period, respectively. The distracted mandibles were harvested after 4 weeks of consolidation and analyzed radiographically, histologically, and immunohistochemically.

RESULTS:

Group III showed significantly increased mineral density, enhanced bone formation, a higher collagen orientation index, and greater expression of type I collagen and osteocalcin proteins.

CONCLUSIONS:

Application of ESWT after active distraction enhances bone maturation and mineralization.


Clinical relevance: Animal study. Bone regeneration – positive outcome for MTS device: dermagold100

Department of Urology, Knuppe Molecular Urology Laboratory, School of Medicine, University of California, San Francisco, CA.

Zhang et al., 2020

Urology. 2020 Apr 10;S0090-4295(20)30357-5. doi:10.1016/j.urology.2020.03.035.

Delayed Treatment With Low-intensity Extracorporeal Shock Wave Therapy in an Irreversible Rat Model of Stress Urinary Incontinence

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Abstract

Objective: To determine the outcomes and mechanisms of delayed low-intensity extracorporeal shock wave therapy (Li-ESWT) in a rat model of irreversible stress urinary incontinence (SUI).

Materials and methods: Twenty-four female Sprague-Dawley rats were randomly assigned into 3 groups: sham control, vaginal balloon dilation + β -aminopropionitrile (BAPN; SUI group), and vaginal balloon dilation + BAPN + treatment with Li-ESWT (SUI-Li-ESWT group). An irreversible SUI model was developed by inhibiting the urethral structural recovery with BAPN daily for 5 weeks. Thereafter, in the SUI-Li-ESWT group, Li-ESWT was administered twice per week for 2 weeks. After a 1-week washout, all 24 rats were evaluated with functional and histologic studies at 17 weeks of age. Endogenous progenitor cells were detected via the EdU-labeling method.

Results: Functional analysis with leak point pressure testing showed that the SUI-Li-ESWT group had significantly higher leak point pressures compared with untreated rats. Increased urethral and vaginal smooth and striated muscle content and increased thickness of the vaginal wall were noted in the SUI-Li-ESWT group. The SUI group had significantly decreased neuronal nitric oxide /tyrosine hydroxylase positive nerves ratio in the smooth muscle layers of the urethra, while the SUI-Li-ESWT group had neuronal nitric oxide/tyrosine hydroxylase+ nerves ratio similar to that of the control group. The continuity of urothelial cell lining was also improved in the SUI-Li-ESWT group. In addition, there were significantly increased EdU-positive cells in the SUI-Li-ESWT group.

Conclusion: Li-ESWT appears to increase smooth muscle content in the urethra and the vagina, increase the thickness of urethral wall, improve striated muscle content and neuromuscular junctions, restore the integrity of the urothelium, and increase the number of EdU-retaining progenitor cells in the urethral wall.

Clinical Relevance: New upcoming indication trend based upon preclinical studies and one clinical trial.

Device: MTS Dermagold device (Atlanta, GA; USA) – Pioneering studies with MTS technology!

European Institute for Sexual Health (EISH), Hamburg, Germany.

Hartmut Porst, 2020

Review of the Current Status of Low Intensity Extracorporeal Shockwave Therapy (Li-ESWT) in Erectile Dysfunction (ED), Peyronie's Disease (PD), and Sexual Rehabilitation After Radical Prostatectomy With Special Focus on Technical Aspects of the Different Marketed ESWT Devices Including Personal Experiences in 350 Patients

Sex Med Rev. 2020 Jun 1;S2050-0521(20)30031-7.

doi: 10.1016/j.sxmr.2020.01.006. Online ahead of print.

Introduction: Although the literature of the positive effects of penile low intensity extracorporeal shockwave therapy is meanwhile substantial, there are substantial differences regarding both the sources of energies and extracorporeal shockwave therapy (ESWT) devices.

Objectives: To provide an overview on the energy range and energy differences of the 6 currently marketed ESWT devices along with personal ESWT experiences in 350 patients.

Methods: This review includes all published preclinical and clinical penile ESWT studies with evaluation of the technical differences of the 6 ESWT devices and the personal experiences with these 6 devices in ED and PD. The main outcomes measures were success rates in ED (International Index of Erectile Function-erectile function change, conversion of phosphodiesterase type 5 inhibitors non-responders) and PD (change in deviation and plaque size), differences of used sources of energy, and energy flux densities (EFDs).

Results: 3 different sources of energies are used, that is electromagnetic, electrohydraulic, and piezoelectric. The devices markedly distinguish in the available spectrum of the EFD ranging between 0.09 and 0.55 mJ/mm². In terms of the biological effects, the relevant energy parameters

are -6 dB and the 5 MPa focus, which differ substantially between the ESWT devices. In addition, a great variability in the treatment protocols and applied energy is obvious. The preliminary own experiences with low intensity extracorporeal shockwave therapy in 160 ED non-responders and 190 patients with PD with success rates of 45% and 47%, respectively, are reported.

Conclusion: Positive results were published with all 6 ESWT devices in question in patients with organic ED but with huge differences regarding the EFD and the total energies applied. There is growing evidence that concentrated treatment protocols and increasing energies may yield better results. In this context, it may be argued that at least some of the published studies were markedly underpowered. Owing to the paucity of published studies, the literature of the effects of ESWT in PD and for penile rehabilitation after pelvic surgery is currently not conclusive.

Clinical relevance:

- *Very good training document on ESWT in sexual dysfunction. Up to date on clinical application, therapeutic effects and detailed description of technical specifications and considerations. MTS urogold100 is described and presented.*
- *This is the first paper in which all manufacturers put the cards on the table in direct comparison of all technical and clinical parameters!*
- *H. Porst introduces an interesting new medical hypothesis: potential biomolecular mechanism how ESWT could improve ED in the "psychogenic" patient population (sympathetic/adrenergic pathway).*

Background info: *H. Porst, MD, is a longtime customer of MTS and founder of the European Institute for Sexual Health (EISH), Hamburg, Germany. The Journal „Sexual Medicine Reviews“ is the official Journal of the International Society for Sexual medicine (ISSM), which arranges an annual congress that MTS usually attends.*

Personal Experience with LI-EWST in ED and Peyronie's Disease

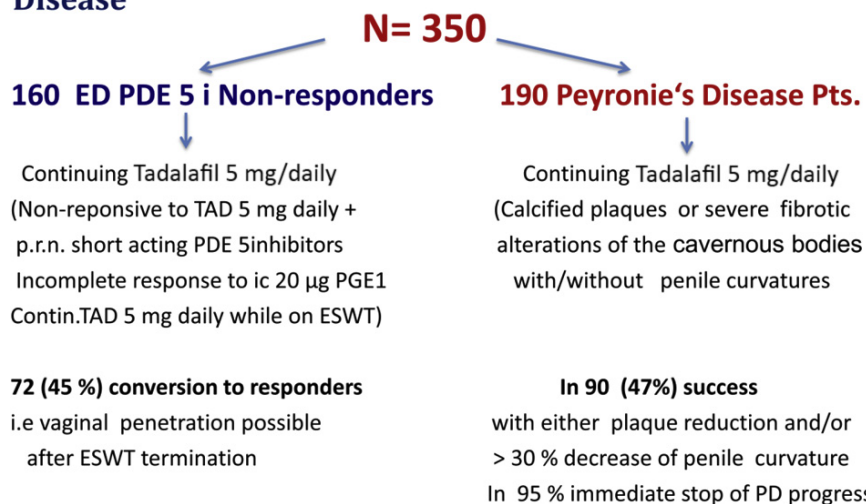


Figure 27. Personal experience with Li-ESWT in ED and PD over the past 4 years. ED ¼ erectile dysfunction; ic ¼ intracavernosal; Li- ESWT ¼ low intensity extracorporeal shockwave therapy; PD ¼ Peyronie's disease; PDE5 inhibitors ¼ phosphodiesterase type 5 inhibitors; PGE1 ¼ prostaglandin E1; p.r.n. ¼ when necessary; TAD ¼ tadalafil.