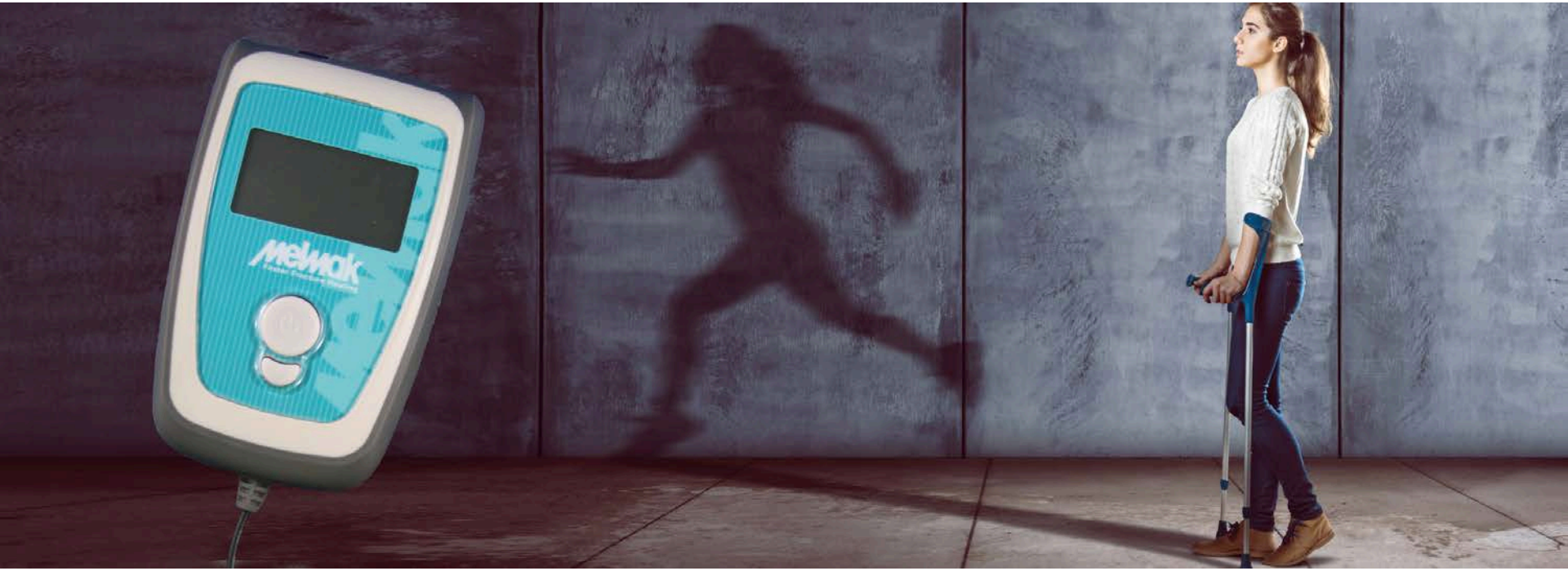
Low Intensity Pulsed Ultrasound



melmak

The successful aid for healing bones.

CONTENT

- Part I: - What is Ultrasound?
  - Studies
- Part II: - Comparison Melmak / Exogen
- Part III: - Indications
  - Target groups / audiences

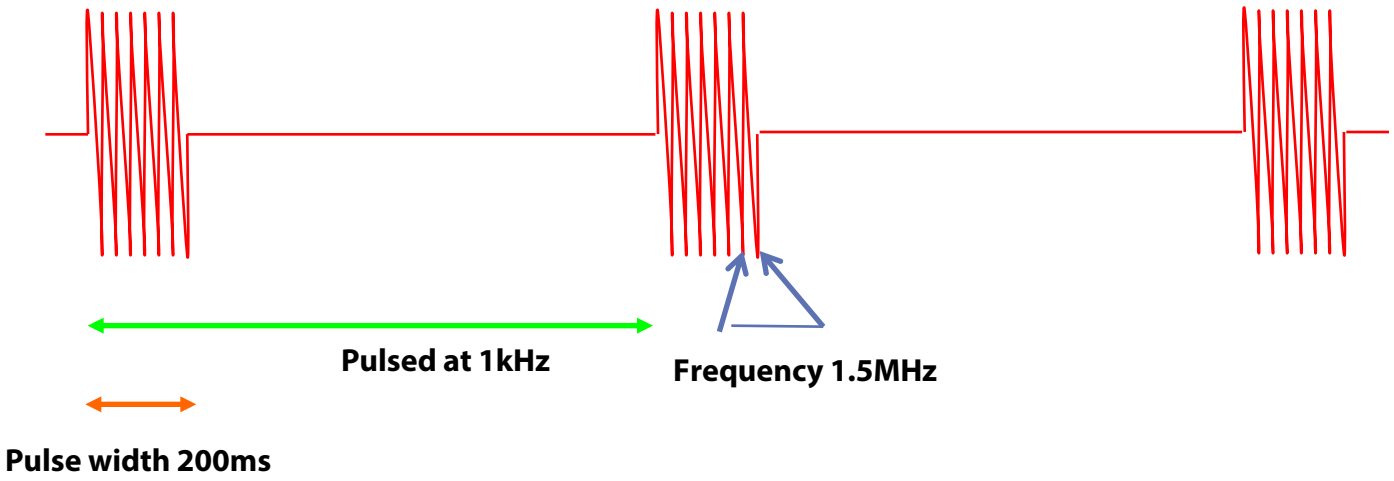
PART I

- **What is Ultrasound?**
- **Studies**

Ultrasound

- Inaudible high frequency mechanical vibrations
  - Above 20kHz
  - Introduced as a therapy over 70 years!
- Mechanical energy transmitted as an acoustical pressure wave
  - Propagated through molecular collision and vibration with a progressive loss in intensity (attenuation) due to absorption and scatter of the wave

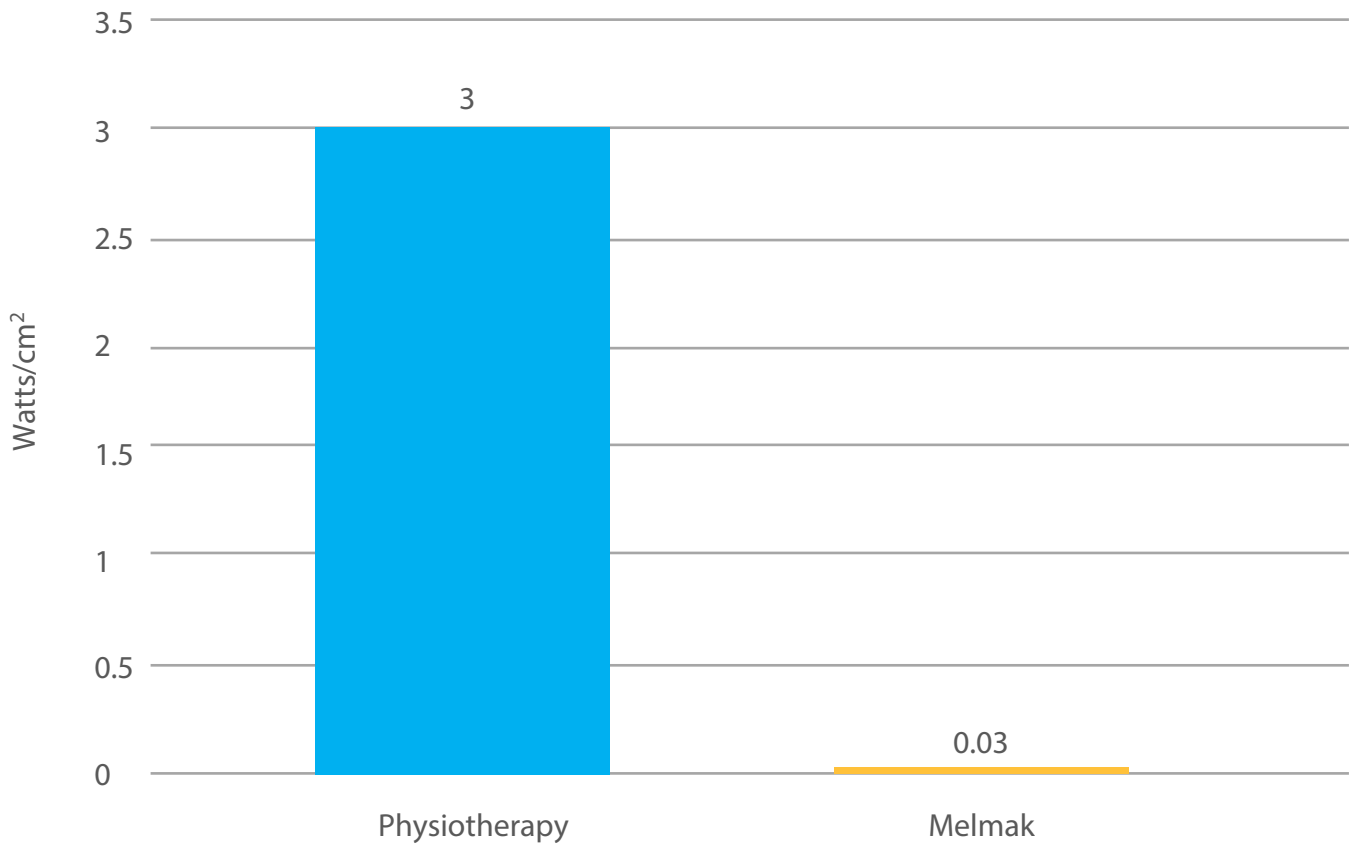
Low Intensity Pulsed Ultrasound

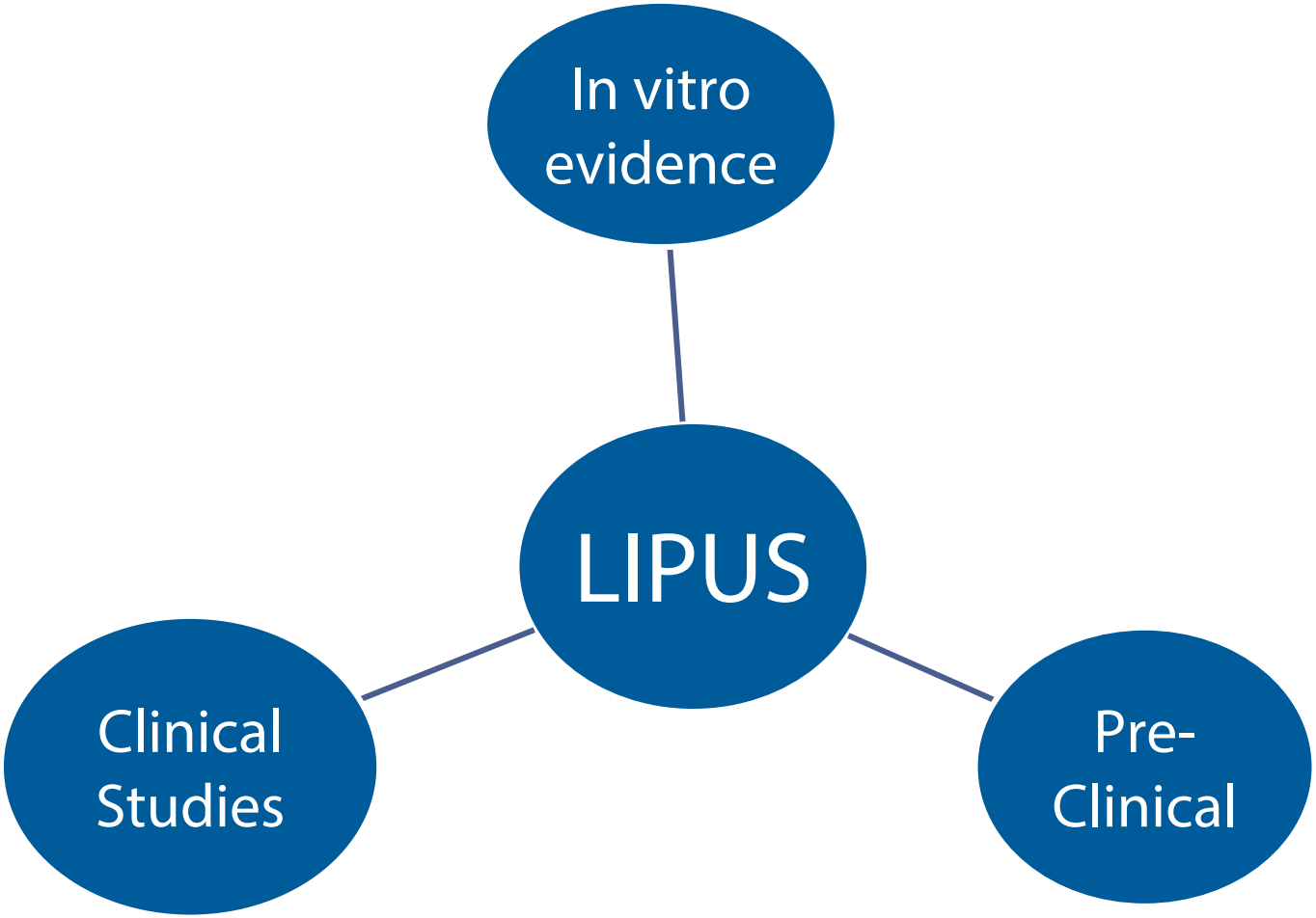


Standard signal and regulatory approved throughout the world to assist with fracture healing

Many studies supporting the biological effects(s) of LIPUS

LIPUS ≠ Physiotherapy Ultrasound




In vitro evidence
LIPUS
Clinical Studies
Pre-Clinical

Studies

- Julius Wolff
  - German anatomist, born March 21, 1835, Märkisch-Friedland in Westpreussen; died February 2, 1902.

Wolff's law stated that every **change in form and function** of a bone, or in its function alone, is followed by certain definite **changes in its internal architecture** and equally definite secondary alteration in its mathematical laws

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Available online at www.sciencedirect.com
ScienceDirect
Life Sciences 79 (2006) 1936–1943

Life Sciences
www.elsevier.com/locate/lifescie

Effects of low-intensity pulsed ultrasound on the differentiation of C2C12 cells

Kyoko Ikeda [a,b], Tadahiro Takayama [a,*], Naoto Suzuki [c,d], Koichi Shimada [a,e], Kichibee Otsuka [c,d], Koichi Ito [a,e]

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[b] Nihon University Graduate School of Dentistry, Tokyo, Japan
[c] Department of Biochemistry, Nihon University School of Dentistry, Tokyo, Japan

In vitro evidence

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Ultrasound in Med. & Biol., Vol. 33, No. 9, pp. 1468–1474, 2007

0301-5629/07/$–see front matter

doi:10.1016/j.ultrasmedbio.2006.12.003

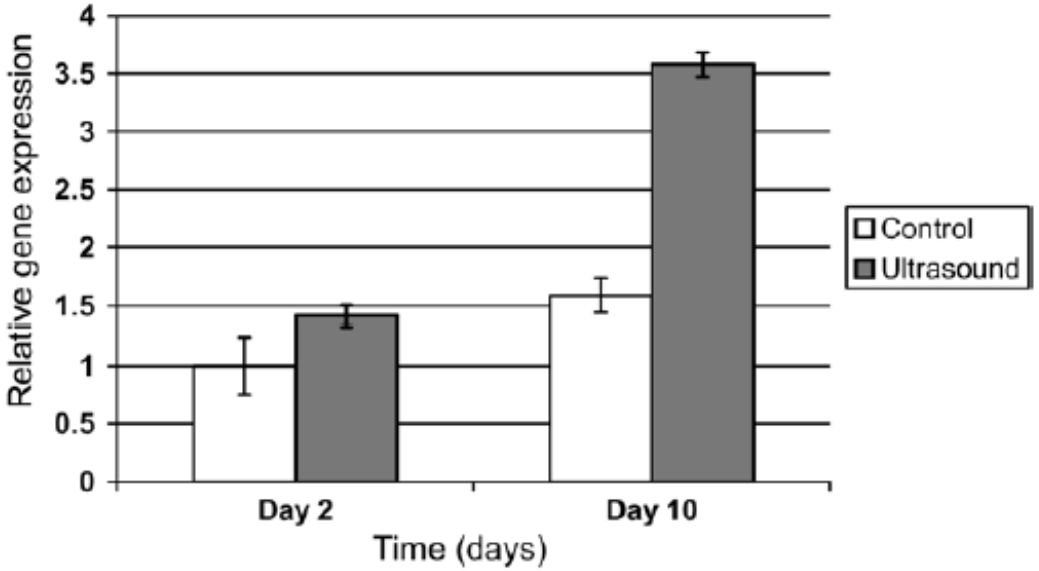
● *Original Contribution*

PULSED LOW INTENSITY ULTRASOUND ENHANCES MINERALISATION IN PREOSTEOBLAST CELLS

JENNY UNSWORTH, SAIRA KANEEZ, SUE HARRIS, JONATHAN RIDGWAY, STEVEN FENWICK, DAVID CHENERY, and ANDREW HARRISON

Smith and Nephew Research Centre, York Science Park, Heslington, York, United Kingdom

(*Received* 9 *May* 2006; *revised* 14 *December* 2006; *in final form* 19 *December* 2006)



In vitro evidence

Fig. 1. Alkaline phosphatase mRNA expression. Effect of low intensity pulsed ultrasound on alkaline phosphatase mRNA expression in MC3T3-E1 cultures at days 2 and 10 using quantitative real-time RT-PCR as described in the materials and methods. Ultrasound was administrated to the cultures for 20 min per d. Expression was normalised to day 2 for control cultures and all subsequent results compared with this.

In vitro evidence

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Available online at www.sciencedirect.com

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Biomaterials 24 (2003) 2379–2385

Biomaterials

www.elsevier.com/locate/biomaterials

Cytokine release from osteoblasts in response to ultrasound stimulation

J.K. Li[a], W.H. Chang[a,*], J.C. Lin[a], R.C. Ruaan[b], H.C. Liu[c], J.S. Sun[c]

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[b] *Department of Chemical Engineering, Chung Yuan Christian University, Chung Li, Taiwan*

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Received 29 October 2002; accepted 19 January 2003

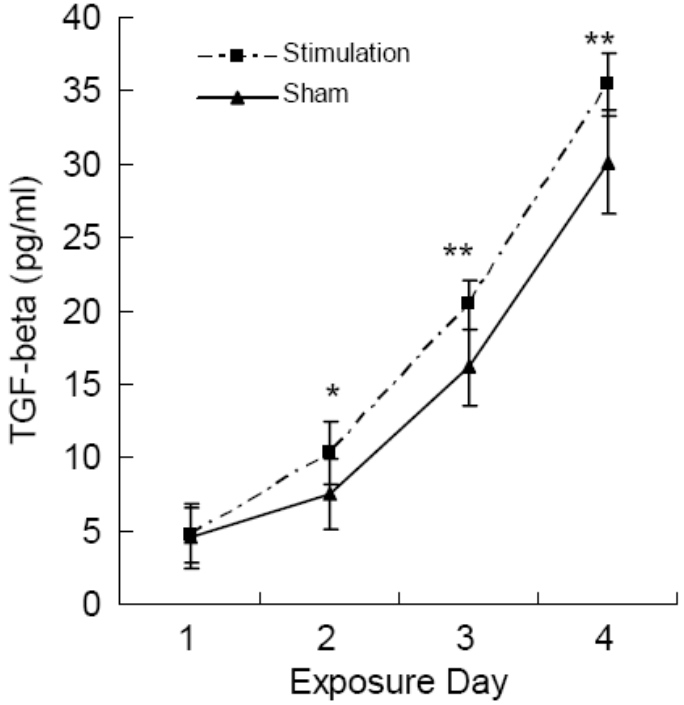


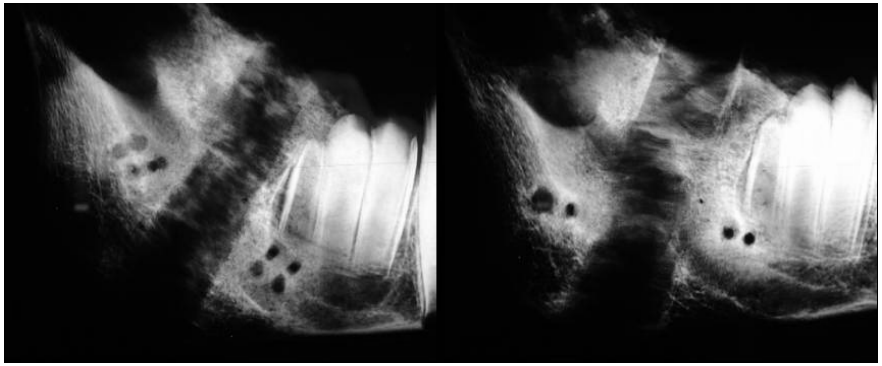
Fig. 5. TGF-β1 concentration per well-analyzed after 1, 2, 3 and 4 days of exposure of osteoblasts to ultrasound or sham exposure for 15 min per day. The symbol $*$ indicates $p<0.05$ ($n=10$) when compared with the sham group, and $**$ means $p<0.01$ ($n=10$) when compared with the sham group.

Pre Clinical Studies

AUTHOR	STUDY	OUTCOME MEASURE	RESULTS
Walsh et al 2007	Effect of US on tendon-bone healing - sheep model	Healing of tendon/ bone junction	improved healing
Cook et al 2001 Clinical orthopaedics and related research	Improved cartilage repair after US - rabbit model	Cartilage Healing	daily US had positive effect on osteochondral damage
Leung et al 2008, Journal of Orthopaedic Research	Low-Magnitude High-Frequency Vibration Accelerates Callus Formation, Mineralization, and Fracture Healing in Rats	acceleration of healing	low-magnitude high-frequency vibration (enhances healing in the closed femoral shaft fracture in rats.
Pilla et al 1990, Journal of Orthopaedic Trauma	Non Invasive Low Intensity pulsed Ultrasound Accelerates Bone Healing in the Rabbit	acceleration of healing	Ultrasound treated bone as strong in torsion as intact fibulae, increased periosteal reaction
Walsh et al 2007, J Biomed Mater Res B Appl Biomater 2007	Effect of low intensity pulsed ultrasound of healing of an ulna defect filled with a bone graft substitute	rate of defect healing	LIPUS resulted in more new bone growth at wk 4 and 12 compared to control and increased VEGF expressionLIPUSPUSth
Walsh et al 2007, Athroscopy	Effects of Low Intensity Pulsed Ultrasound on Tendon Bone Healing in an Intra articular sheep knee model	Healing at tendon/bone junction	LIPUS resulted in improved ability to withstand increased load at tendon/bone junction
Lu et al, 2008 Ultrasound in Medicine	Low Intensity Pulsed Ultrasound Accelerated Bone tendon junction healing through regulation of vascular endothelial growth factor expression and cartilage formation	Healing of tendon/ bone junction	LIPUS resulted in enhanced healing at bone/tendon junction
Cook et al, 2001 Clinical Orth and Related Research	Improved Cartilage Repair After Treatment with Low Intensity Pulsed Ultrasound	Healing of Osteochondral Defect	Ultrasound treatment significantly improved the morphologic features and histologic characteristics of the repair cartilage

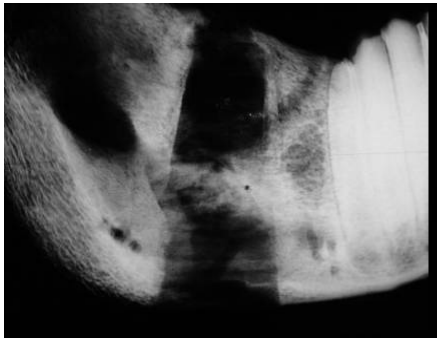
Pre Clinical Studies

- Evaluation of external ultrasound stimulation and growth factors on bone healing during distracting of the mandible, Stephens, et al, 2005

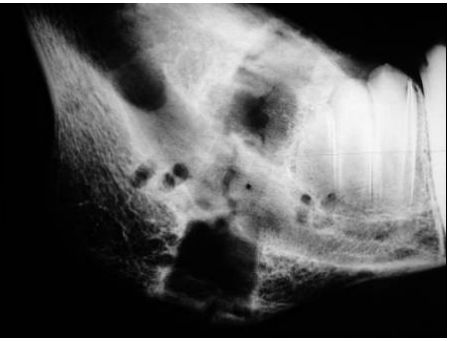


Day 25: 1 mm per day

Day 25: 1 mm per day + LIPUS



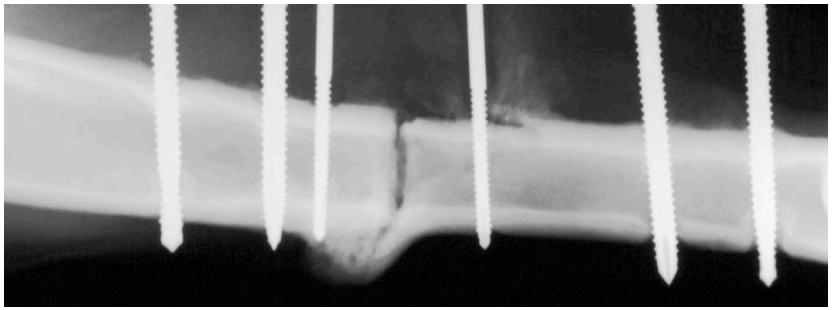
Day 25: 3 mm per day



Day 25: 3 mm per day + LIPUS

Pre Clinical Studies

HANTES, MD et al, 2004



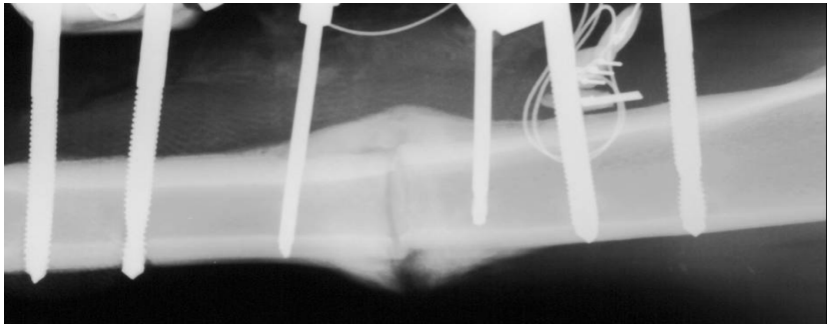


Fig. 4-B
In contrast, in the treatment group the callus is more dense and homogeneous with a large **diameter.**

Human – Clinical

. . .

Burden of Proof

Tokai J Exp Clin Med., Vol. 32, No. 4, pp. 121-125, 2007

Effect of Low-Intensity Pulsed Ultrasound Treatment for Delayed and Non-union Stress Fractures of the Anterior Mid-Tibia in Five Athletes

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[1] *Department of Orthopaedic Surgery, Surgical Science, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan*
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J Orthop Sci (2007) 12:35–41
DOI 10.1007/s00776-006-1080-3

JOURNAL OF
ORTHOPAEDIC SCIENCE

Original article

Low-intensity pulsed ultrasound treatment for postoperative delayed union or nonunion of long bone fractures

SEIYA JINGUSHI[1], KOSAKU MIZUNO[2], TAKASHI MATSUSHITA[3], and MORITOSHI ITOMAN[4]

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[2]Kobe Rosai Hospital, Kobe, Japan
[3]Department of Orthopaedic Surgery, Teikyo University School of Medicine, Tokyo, Japan
[4]Department of Orthopaedic Surgery, School of Medicine, Kitasato University, Sagamihara, Japan

Part I - Studies

Eur J Orthop Surg Traumatol (2005) 15: 244–246
DOI 10.1007/s00590-005-0235-9

CASE REPORT

Takaaki Fujishiro · Nobuzo Matsui · Shinichi Yoshiya
Hiroyuki Fujioka · Masaya Tsunoda
Masahiro Kurosaka

Treatment of a bone defect in the femoral shaft after osteomyelitis using low-intensity pulsed ultrasound

Ultrasound in Med. & Biol., Vol. 31, No. 10, pp. 1391–1402, 2005

0301-5629/05/$–see front matter

ELSEVIER

doi:10.1016/j.ultrasmedbio.2005.06.002

● *Original Contribution*

LOW-INTENSITY PULSED ULTRASOUND: EFFECTS ON NONUNIONS

DIETER GEBAUER,* EDGAR MAYR,† ERNST ORTHNER
*Orthopädische Klinik Tegernsee, Tegernsee, Germany; †Zentralklinikum
Germany; ‡Krankenhaus der Barmherzigen Schwestern vom Heiligen Gei
§Exogen Inc., Piscataway, NJ, USA

International Orthopaedics (SICOT) (2005) 29: 121–124
DOI 10.1007/s00264-004-0625-3

ORIGINAL PAPER

Hani El-Mowafi · Mona Mohsen

The effect of low-intensity pulsed ultrasound on callus maturation in tibial distraction osteogenesis

Knee Surg Sports Traumatol Arthrosc
(2004) 12: 162–164

DOI 10.1007/s00167-003-0425-0

SPORTS MEDICINE

Hiroyuki Fujioka
Juichi Tanaka
Shinichi Yoshiya
Masaya Tsunoda
Kenji Fujita
Nobuzo Matsui
Takeshi Makino
Masahiro Kurosaka

Ultrasound treatment of nonunion of the hook of the hamate in sports activities

Busse et al., Meta analysis

Table 1: Summary of the trials included in the meta-analysis

Trial	Location of fracture	Sample size, no. of fractures		Mean age (and SD), yr	Male: female ratio	Fracture		Mean time to healing (and SD), d		Effect size	Quality score†
		Treatment group	Control group			Open	Closed	Treatment group	Control group		
Heckman et al[39]	Tibial shaft	33	34	Treatment 36 (2) Control 31 (2)	54:13	3 (grade I)	64	114 (7.5)	182 (15.8)	5.41	5
Kristiansen et al[40]	Distal radius	30	31	Treatment 54 (3) Control 58 (2)	10:51	0	61	61 (3)	98 (5)	8.82	5
Mayr et al[42]	Scaphoid	15	15	37 (14)	25:5	NA	NA	43 (11)	62 (19)*	1.20	4

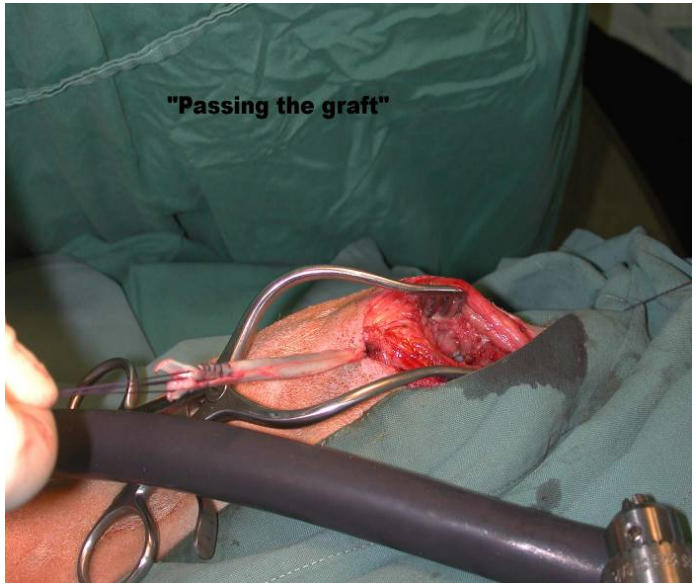
Note: SD = standard deviation, NA = not applicable.
*Healing time was defined as the time from initiation of treatment to removal of the cast.
†Maximum score 5 (see Methods section).

New Indications

• • •

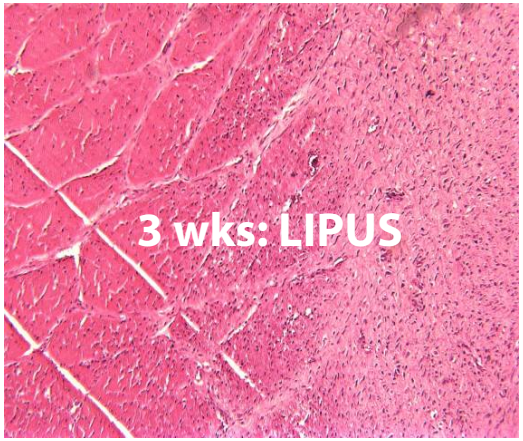
Tendon Bone Healing

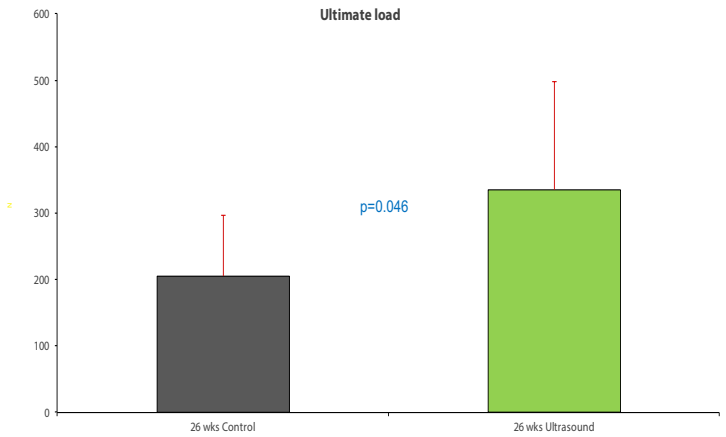
- Effects of low intensity ultrasound on tendon bone healing
  Walsh, WR et al 2007



Tendon Bone Healing (cont.)

- Improved healing at tendon bone interface for soft tissue grafts
- Increased integration between tendon and bone
- Improved mechanical properties of graft
- Conclusion: Indications of low intensity pulsed ultrasound maybe expanded to include tendon-bone healing
  - RC repair
  - ACL repair





Rotator Cuff

The Effects of Low-Intensity Pulsed Ultrasound on Tendon-Bone Healing in a Transosseous-Equivalent Sheep Rotator Cuff Model

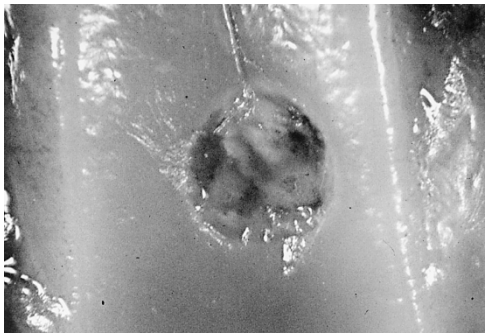
Running title: Effect of LIPUS on T-B Healing

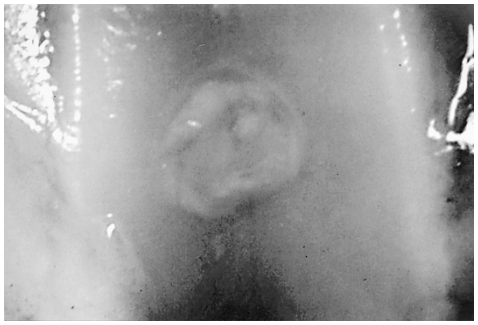
Vedran Lovric BE MBiomedE, Michael Ledger MD, Jerome Goldberg MD, Wade Harper MD, Yan Yu PhD, Nicky Bertollo PhD, Matthew Pelletier PhD, Rema Oliver PhD, and William R. Walsh PhD

Cartilage / Chondral

The Effect of Low-Intensity Pulsed Ultrasound on Autologous Osteochondral Plugs in a Canine Model, Cook et al 2008

- Low-intensity pulsed ultrasound improved interface cartilage repair of autologous osteochondral plugs compared with controls in a canine model.





4 weeks of daily ultrasound

PART II

Comparison
Melmak vs. Exogen

Pro & Contra
Exogen Money Back Guarantee

- It is legally not always allowed (e.g. in Germany it is forbidden to give a healing guarantee – and this could be one!)
- Patient has to prove that the device is used according the instructions etc.

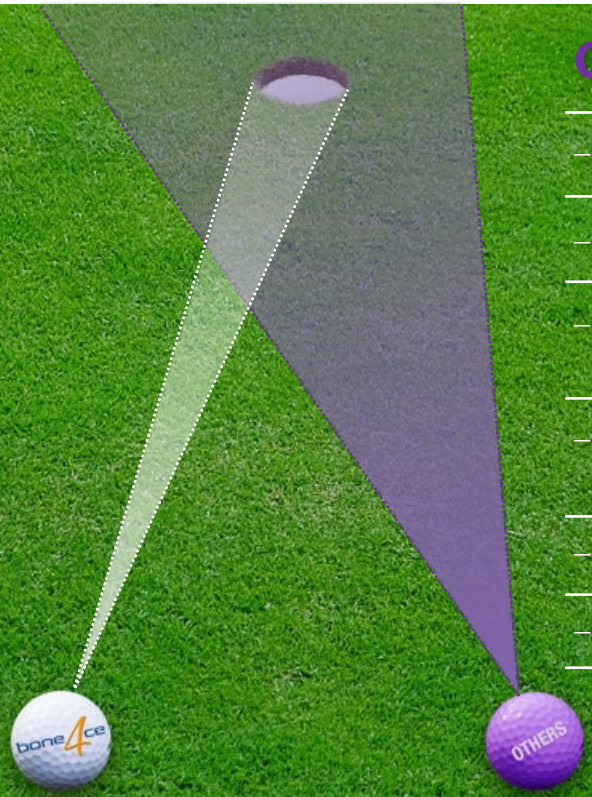
It is **your decision** as a distributor which strategy you want to use in your market!

You can do it in a similar way but as **WE ALWAYS WANT to act better** - BTT is following a different strategy.

Precision is always better.

Melmak

- ✓ SATA 30 mW/cm² **+/-10%**
- ✓ Acoustic power 118 mW **+/-10%**
- ✓ 2 Transducer sizes for convenient adjustment
- ✓ Each device individually calibrated
- ✓ Higher amounts of treatment
- ✓ Multiple and single patient devices
- ✓ Circuit board Made in Germany

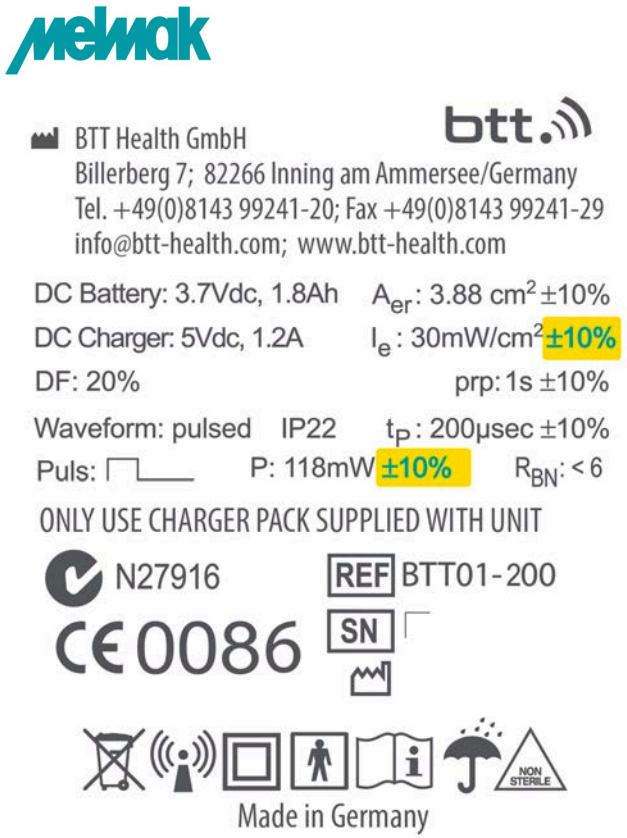


Others

- – SATA 30 mW/cm² **+/- 30%**
- – Acoustic power 117 mW **+/- 30%**
- – 1 Transducer size only
- – Due to high tolerance mass production without individual calibration
- – Less amount of treatments
- – Single patient devices only

Melmak – High accuracy for best results.

The quality difference is in the signal



Exogen

Technical specification (out of their IFU)

- EXOGEN Operating Specifications
- Modulating signal burst width 200+/- 10% microsecond (µs)
- Repetition Rate 1.0+/- 10% kilohertz(kHz)
- Duty Factor 20%
- Effective radiating area (ERA) 3.88 +/- 1% square cm (cm^2)
- Spatial avg.-temporal avg. (SATA) 30 **+/- 30%** mW/cm^2
- Temporal average power 117 **+/- 30%** milliwatts(mW)
- Beam non-uniformity ratio (BNR) 4.0 maximum
- Battery 3.7 VDC, 700 mAh
- Battery Type Lithium-ion
- Input Voltage (USB) 5.0 VDC, 2.6A max.
- Beam type Collimated

Strategy of BTT Health

- Biggest interest of a patient is to be healed!
- It is not their interest to get their money back!
- Depending on your price / treatment you can calculate when your device is fully paid
- A patient will get a device for free until the healing occurs (customers will ask for that perhaps once/year every 80,000 treatments)

Comparison

identical indications
identical usage
identical ultrasound signal
but…

Melmak	Exogen
• TWO transducer sizes (small & large) • ONE single device **for all fractures** • Devices with – 200, – 350 and – 1500 treatments	• ONLY one small transducer with • **For each fracture** one device (e.g. with most broken shoulders) • ONLY one type of treatment

Transducer – small AND large

- To allow improved handling depending on where the fracture is and how old the patient is.

- Technical structure “inside”: the signal and the intensity are the same, only the housing of the transducer and the transducer holder are of different sizes.

Why small?

- Especially for fractures at the smaller extremities like foot/ankle, hand, shoulder.
- It stays better in position and is reducing the load on the fracture.
- More convenient for the patient.

Why large?

- Easier to adjust and to correct the position at all other areas
- **Easier handling** particular **for** especially **elderly patients**

Different numbers of allocated treatments

Melmak

A version e.g. with 1,500 or 350 programmed treatments allows renting the device to:

- different patients or
- usage in a hospital **with a number of different users/per day** or
- **one patient with several/ multiple fractures (e.g. shoulder)**
- Additionally 200 treatment device for single patient use!

Exogen

Only single patient devices!
Exogen is **not offering** a version with a **higher amount of treatments**.

Means:

Four fractures -

four different devices

Part III

- **Indications**
- **Target groups / Audiences**

Ease of Use

- Non invasive
- Application over fracture site
- 20 minute treatment daily

Low Intensity Pulsed Ultrasound – LIPUS

Increases

- Gene expression
- Secretion of growth factors
- Ossification
- Blood flow
- Number of stem cells at fracture increases proliferation of stem cells into bone

Indications

where bone is needed to form/heal/remodel

Bone and Soft Tissue Indications

- Fresh fractures
- Delayed unions
- Non Unions
- To promote healing at boney / tendon junction

Special Indications

- **Delayed unions**
- **Pseudarthrosis** – AND
  even with **very long lasting Pseudarthrosis**

We have seen very good results and studies have supported this as well. The treatment time will be longer but the result is achieved in moist of the cases.

- Because of the healing rate of above 90 % (a stay in hospital is far more expensive than a treatment with LIPUS)

Target Audiences

Quicker fracture healing is very important for

- Entrepreneurs
- People who have a job with high responsibility and need to be able to work quickly again
- Sport professionals – in many cases paid by the employer
- Police employees
- Army employees

Benefits for Patients

- Quicker bone healing
  (between 30 to 50 % faster recovery time)
- Extremely successful track record for solving delayed unions and healing Pseudarthrosis (10 % of all fractures)
- **Earlier back to the job**
- **Ease of use**
- **No side effects**

Benefits for Distributors, Patients, Health Insurance

Several options for a distributor –

- a straight forward sale without any additional effort for refurbishment if sold as single patient device

- Patients get a brand new and not a refurbished device, single patient device e.g. 200 or 350 treatments

- AND offering the solution for those who need more treatments per device like hospitals or rehab institutions.

Conclusion I

- 20 minute treatment daily
- Small and large transducer
- Will assist every stage of healing
  (even long lasting Pseudarthrosis)
- Hospital or/and Patient
- Purchase or rental options
- Different treatments – one device
- Specific clinician software for treatments

Conclusion II

- Melmak - effective for accelerating fracture healing by 38%
  (results from studies performed with Melmak signal)
- Melmak - average healing rate of 86% for non unions
  (results from studies performed with Melmak signal)
- Consider as a first option for the management of fractures, delayed unions and non unions
- Achieves similar healing rates to surgery, BMPs, implanted bone stimulators without associated risks, complications and cost

Thank you for your attention.

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BTT01-350, V1 – 2017-12-22