Evidence For and Against Effectiveness of Low Intensity Pulsed Ultrasound for Bone Fracture Healing

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Relevance of musculoskeletal disorders

Proportion of United States Population Reporting Chronic Medical Conditions, 2012

- Musculoskeletal: 54%
- Circulatory: 31%
- Respiratory: 28%
- Diabetes: 13%
- Cancer: 9%

Source: National Center for Health Statistics, National Health Interview Survey, 2012
Bone Regeneration

- Bone has the unique capacity of **scarless regeneration & recovery to full functionality**

Reproduced from Giannoudis et al., 2007
Phases of Fracture Healing

I. Haematoma formation, inflammation,
   → recruitment of osteogenic precursor cells

II. Angiogenesis, cell proliferation osteogenic differentiation
   → Intramembranous ossification

III. Chondrogenesis, maturation of osteoblasts
   → Endochondral ossification

IV. Cell maturation
   → Remodeling
Bone fracture treatment complications

Tibia shaft fracture

Malunion            Delayed/ nonunions        Infections        Large defects

Malunion          Delayed/ nonunions            Infections        Large defects

FIG. 5. Combined complications of delayed union, nonunion, malunion and total infection for each treatment method.

Coles & Gross JCC, 2000
Low Intensity Pulsed Ultrasound

• is an add-on treatment and portable device

• is used to promote bone healing by stimulating bone growth (osteogenesis)

• applications
  • operatively or non-operatively managed fractures
  • osteotomies (cutting of a bone)
  • Delayed unions and nonunions

• costs
  • $1500 to 7000 USD (purchase)
  • some devices can be re-used
  • Health insurance may or may not cover the cost of the device

1994 FDA premarket approval
• fresh, closed, posteriorly displaced distal radius fractures
• fresh, closed or grade I open tibial diaphyseal fractures

2000
• established nonunions, excluding skull and vertebra
Low Intensity Pulsed Ultrasound - Definition

- **Ultrasound** waves with frequencies above the audible range are used

  \[ 100 \text{ kHz} \leq f \leq 10 \text{ MHz} \]

- **Low Intensity** level (spatially and temporally averaged) between those used for diagnostic and therapeutic ultrasound applications,

  \[ 5 \text{ mW/cm}^2 \leq I_{sata} \leq 100 \text{ mW/cm}^2 \]

- **Pulsed** bursts of acoustic waves are applied at a Pulse Repetition Frequency (PRF) and Duty Cycle (DC) for a specific time

  \[ 100 \text{ Hz} \leq \text{PRF} \leq 1 \text{ kHz} \]
# Most common LIPUS protocol

<table>
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<tr>
<th>Parameter</th>
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<td><strong>Transducer</strong></td>
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<td>( f = 1.5 \text{ MHz} )</td>
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<tr>
<td><strong>Intensity</strong></td>
<td>( I_{\text{SATA}}=30 \text{ mW/cm}^2 )</td>
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<td><strong>Duration</strong></td>
<td>1 x 20 min /day for up to several months</td>
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Exogen's Sonic Accelerated Fracture Healing System (SAFHS) (Exogen, Inc, Piscataway, NJ)
Mechanical effects introduced by a pulsed acoustic field

- **Ultrafast:** Oscillatory Strain at Ultrasound Frequency
- **Fast:** Acoustic Radiation Force at Pulse Repetition Frequency
- **Slow:** Acoustic Streaming
LIPUS studies…

…discussed in this talk

In vitro


• 211 (mainly in-vitro) studies

In vivo (systematic reviews and meta-analyses)

Leighton et al. *Injury* (2017)
Rutten et al. *JBJS Reviews* (2016)

… for comparison

ISI Web of Science, March 2018
Intrinsic problems with the application of LIPUS

• correct application by patient
  ➢ positioning, coupling

• limited adherence to treatment
  ➢ inconvenient application 20min/day over months
  ➢ need to carry device, blocks daily activity

• sound attenuation / reflection in variable amounts of soft/callus tissues / implants
  ➢ acoustic dose at fracture site?
Status quo of clinical trials on LIPUS treatment

- most randomized controlled trials RCTs are described for fresh fractures

- often low number of cases: N = 8 – 500 (TRUST study)

- “... RCTs on LIPUS treatment are poorly reported, lack outcomes important to patients, and are at high risk of bias.” (Schandelmair et al., 2017)

- almost no RCTS for delayed- and non-unions

- most of the clinical studies are funded by the producer/manufacturer
  - “... only 12% (3/26) of trials were free from industry funding” (Schandelmair et. al., 2017)
Intrinsic challenge of clinical LIPUS trials for nonunions

• when a non-union is established, surgery is a first-line treatment.
• LIPUS is advised only if all the procedures failed / too risky.

No Data: 1st surgery vs LIPUS
revision surgery vs LIPUS

• surgeons are reluctant to undertake an RCT treating nonunion without surgery
• Institutional Review Boards may be reluctant to approve such RCTs
• patient recruitment for an operative vs non-operative treatment protocol is difficult (Leighton et al., 2017)

➢ there is currently no way to evaluate the „perfect time“ to initiate LIPUS treatment
<table>
<thead>
<tr>
<th>Trials</th>
<th>Cases</th>
<th>LIPUS vs sham or no device</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schandelmaier et al. <em>BMJ</em> (2017)</td>
<td>26 RCTs</td>
<td>1594 min: 8 max: 501</td>
<td>• all trials&lt;br&gt;  ➢ reduction to full load bearing, pain, radiographic healing&lt;br&gt;  ➢ 4 trials with low risk of bias&lt;br&gt;  ➢ no LIPUS effect&lt;br&gt;  ➢ moderate quality evidence that LIPUS has no effect</td>
</tr>
<tr>
<td>Lou et al. <em>Medicine</em> (2017)</td>
<td>12 RCTs</td>
<td>1099</td>
<td>➢ reduction of time to fracture union&lt;br&gt;  ➢ improved quality of life&lt;br&gt;  ➢ No effects on time to work and full weight bearing, and incidence rate of delayed or nonunions</td>
</tr>
<tr>
<td>Leighton et al. <em>Injury</em> (2017)</td>
<td>13 NRCTs</td>
<td>1441</td>
<td>➢ LIPUS effect size 82-84%&lt;br&gt;  ➢ hypertrophic &gt; atrophic&lt;br&gt;  ➢ &lt;6 months from surgery favorable</td>
</tr>
<tr>
<td>Rutten et al. <em>JBJS Reviews</em> (2016)</td>
<td>24 RCTs</td>
<td>429</td>
<td>➢ Reduced healing time (39.8 days)&lt;br&gt;  ➢ 3 RCTs: no effect for return to work&lt;br&gt;  ➢ 2 HQ RCTs:&lt;br&gt;  ➢ Enhanced bone formation in delayed/impaired cases&lt;br&gt;  ➢ No prevention of delayed or nonunions</td>
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**Low quality evidence from (26 trials):**
- possible reduction of days to full weight bearing, pain
- large reduction in time to radiographic healing
  - No effects for subgroups (only analyzed for radiographic healing)
  
   *(management type / stress fractures / nonunion / osteotomy)*

**Moderate quality evidence:**
- no effect on time to return to work or the number of subsequent operations
- no effect on days to radiographic healing

**High quality evidence (4 trials, only fresh fractures):**
- no effect on pain reduction, days to full weight bearing, or adverse effects related to the device

- **Strong recommendation against LIPUS**

<table>
<thead>
<tr>
<th>Included</th>
<th>LIPUS/Sham</th>
<th>Mean Age</th>
<th>Type</th>
<th>Primary Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Busse, 2014</td>
<td>(23/28)</td>
<td>40</td>
<td>Fresh Fracture</td>
<td>Operative</td>
</tr>
<tr>
<td>Busse, 2016</td>
<td>(250/251)</td>
<td>40</td>
<td>Fresh Fracture</td>
<td>Operative</td>
</tr>
<tr>
<td>Emani, 1999</td>
<td>(15/17)</td>
<td>37</td>
<td>Fresh Fracture</td>
<td>Operative</td>
</tr>
<tr>
<td>Lubbert, 2008</td>
<td>(61/59)</td>
<td>38</td>
<td>Fresh Fracture</td>
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<td>Heckmann, 1994</td>
<td>(48/49)</td>
<td>33</td>
<td>Fresh Fracture</td>
<td>Non-Operative</td>
</tr>
<tr>
<td>Kristiansen, 1997</td>
<td>(40/45)</td>
<td>56</td>
<td>Fresh Fracture</td>
<td>Non-Operative</td>
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is based on 4 „low risk“ studies (N = 349/355) including

- young population
- primary treatment with lowest complication rate (reamed nails)
Moderate to high-quality evidence (12 RCTs):

- reduces the time to fracture union
- improves the quality of life (SF-36)
- does not affect functional recovery (time to return to work / full weight bearing)
- does not reduce incidence rate of delayed union and nonunion.

Recommendations: LIPUS may be better for …

- fractures with conservative treatment than those with operative treatment.
- upper limb fractures than lower limb fractures

LIPUS may not necessarily reduce the incident rate of delayed union and nonunion.

Low to moderate quality evidence (MINORS score for NRCTS):

- LIPUS effect size 82-84%
- effect larger in hypertrophic than in biologically inactive atrophic nonunions
- <6 months from surgery favorable

**Recommendations**

LIPUS can heal without concurrent surgery (but RCTs are needed for confirmation)

LIPUS should be used for nonunions

- as alternative rather than an adjuvant to surgery, if
  - LIPUS treatment starts immediately after the diagnosis of the nonunion
  - the nonunion is biologically active
  - surgery is high risk
Summary of factors that influence LIPUS outcome

Fixation type

- Higher failure rate for non-unions stabilized by intramedullary nail in comparison to plate & screw and external fixator (Watanabe et al., 2013, Lou et al. 2017)

  ➢ Due to intrinsic failure rate difference or interaction of sound wave with implant?

Amount of soft tissue

- "Success rates of delayed unions were lower for deeper bones like the femur and humerus than for subcutaneous bones like the tibia/fibula and radius/ulna." (Mayr et al., 2000)

  ➢ We need a target „acoustic dose“ instead of instrument output values!

Biological competence

- Hypertrophic non-unions (biologically active) benefit more from LIPUS treatment than atrophic ones (Leighton et al., 2017)

  ➢ LIPUS cannot bypass biological component of bone regeneration
Additional co-factors that affect LIPUS outcome

Age, sex, and risk factors (e.g., smoking) can significantly influence bone healing

• "Larger differences between LIPUS and control groups were noted for females (50%), older patients (45%), distal fractures (41%), oblique fractures (46%), larger fractures (45%), and absence of fibular fractures (58%)...“ (Watanabe et al., 2010)

• Patient age was associated with failure to heal among chronic nonunions (Zura et al. 2015)

➢ Is current LIPUS protocol optimal for all cases?
In-vivo studies in animals
LIPUS enhances bone regeneration

- Proven across different species: rat, rabbit, dog, sheep
  
  a) Radiographically
  
  [Images of radiographs showing bone healing]
  
  (Azuma et al., 2001)

  b) Histologically

  [Images of histological sections showing bone healing]
  
  (Hasuike et al., 2011)

  c) Biochemically
  
  d) via Mechanical Testing

- Effects observed at each stage of bone healing *in vivo* in rat femur fracture (Azuma et al., 2001)

- However, lack of mechanistic studies (i.e., targeting bio-physical mechanisms)

» Challenge: Animal vs Transducer size
Problem of LIPUS stimulation in small animals

Exogen’s Sonic Accelerated Fracture Healing System (SAFHS) (Exogen, Inc, Piscataway, NJ)

Charité Focused Imaging & Stimulation System (Berlin, Germany)
In-vitro cell stimulation studies
Summary of *in-vitro* findings

- **In-vitro** studies suggest favorable impact of LIPUS during all phases of bone healing

- However, often studies report controversial effects (e.g., proliferation and differentiation of osteoprogenitors)

**Inconsistency could be caused by**

- Physical artefacts in Set-Ups (standing waves, heating, …)
- Species dependent effects
- Cell-origin (site) specificity
- LIPUS parameters

**Effects induced by in-vitro artefacts may not occur in vivo**

Padilla and Puts *et al.*, 2014
## Most common LIPUS protocol

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**In Vivo**

- FDA approved Exogen's Sonic Accelerated Fracture Healing System (SAFHS) (Exogen, Inc, Piscataway, NJ)
- Ikeda *et al.*, 2006

**In Vitro**

- Sena *et al.*, 2005
Problems with common in-vitro setups

Near Field Interference

Ring Interference and Standing waves

Temperature elevation for various LIPUS setups

Reported effects & intensity level are usually not those experienced by cells.

Hensel et al., 2011

Leskinen & Hynynen, 2012
Alternative – Focused LIPUS

FLIPUS Cell Culture Stimulation Setup

Puts et al. IEEE TUFFC (2016)
Age-dependent differences upon LIPUS exposure *in vitro*

In young rMSCs, osteogenic differentiation enhanced when low LIPUS dose (11.7 mW/cm²), whereas in old rMSCs when high dose (44.5 mW/cm²) applied.

**Drop in Osteogenic Potential of MSCs with Age**

<table>
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<tr>
<th>Age</th>
<th>Osteocalcin</th>
<th>RUNX2</th>
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<td>Young</td>
<td><img src="chart-osteocalcin-young.png" alt="Graph" /></td>
<td><img src="chart-runx2-young.png" alt="Graph" /></td>
</tr>
<tr>
<td>Old</td>
<td><img src="chart-osteocalcin-old.png" alt="Graph" /></td>
<td><img src="chart-runx2-old.png" alt="Graph" /></td>
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Puts et al., 2016, UMB

n = 9, *p < 0.05
Effects under Compromized Physiological Conditions *in vitro*

- **Proliferation** of murine MC3T3-E1 preosteoblasts is **enhanced after FLIPUS** treatment when cells are in **Starving (2% FCS)** medium conditions.

- Similar results observed for **rat MSCs**

*Puts et al., 2014, IEEE International Ultrasonics Proceedings*
LIPUS supports endogenous regeneration from the mechanical side.

The effect of LIPUS is limited if:

- All conditions are already very good
- Handshake between mechanical, biological, structural and biochemical environments is compromised
Conclusions

Basic Science Level

• mechanisms of action, optimal acoustic dose and influencing factors are on the way to be established using improved technology
• establish target dose measures

Translation to Clinical Application

• identify cases, for which LIPUS may / may not have an effect
• identify case and patient specific acoustic doses
• improve technology (e.g. wearable focused array technology)
• combine LIPUS with biological (cell) and chemical (growth factors) treatments
Conclusions

Clinical Studies

• more large scale high-quality “… studies are needed to determine the clinical circumstances under which LIPUS is truly valid and to examine the optimal approach for the use of this adjunctive therapy.” (Lou et al. 2017)

• these studies should…
  – target specific cases
  – assess multiple outcome parameters, including patient benefits
  – assess cost-effectiveness

➤ Our current level of evidence is still positive, but sparse and weak