Low Intensity Pulsed Ultrasound

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Introduction

Sound consists of a series of longitudinal pressure waves travelling through gases, plasmas, liquids or solids. The medium is periodically displaced by the sound waves and so oscillates resulting in local regions of compression and rarefaction. In solids only sound can be transmitted as both longitudinal and transverse waves. The energy carried by the sound waves converts back and forth between the potential energy of the longitudinal wave in the medium / tissue (or lateral displacement strain of transverse waves in solids e.g. bone) and the kinetic energy of the oscillations of the medium / tissue.

The velocity of sound is not dependent upon the frequency but only upon the density of the medium through which it travels. Sound travels at 330m/s (767 mph) in air, 1500m/s (3315 mph) in soft tissue and 3400m/s (7600 mph) in bone.

Depending upon the frequency, sound may be divided into 3 main categories:

1) Infra-sound – frequencies below 20Hz
2) Human audible sound – frequencies between 20Hz and 20KHz
3) Ultra-sound – frequencies over 20KHz.

What is ultrasound?

In the therapeutic setting ultra-sound may be described as mechanical acoustic energy emitted from a piezo-electric transducer which is received by the tissues as a series of pressure waves. These pressure waves are absorbed at a rate proportional to the density of the tissues and cause these tissues to oscillate at an amplitude dependent upon the tissue density, with dense tissues oscillating at a lower amplitude than the less dense tissues. This results in complex gradients of acoustic pressure causing micro-mechanical strains, molecular vibrations and collisions within the tissues with the greatest mechanical strains occurring at the interface between tissues of different densities. These interfaces are commonly present in healing tissues such as the bone / collagen interface of early callus and at bone / tendon junctions (BTJs).

Ultra sound is divided into the 4 main categories of surgical, diagnostic, therapeutic and LIPUS, however as the use of surgical US and diagnostic US are outside the scope of this article we will concentrate on the other two areas:

Therapeutic US

This is traditionally applied at frequencies ranging between 0.75-3MHz, at intensities >100mW/cm² and may be applied in continuous mode or pulsed at 1:1 to 1:4. The transducer head needs to be manually moved over the area being treated in order to prevent potential thermal damage to the tissues. An Ultra-Sound medium such as water-based gel is commonly used at the transducer / skin junction to enable efficient sound conduction through the skin to the underlying tissues.

Low Intensity Pulsed Ultra-Sound (LIPUS)

This consists of frequencies usually ranging from 0.75-1.5 MHz at intensities <100mW/cm² (usually about 30mW/cm²) and usually pulsed at 1:4. The transducer head is strapped or otherwise held in place and remains stationary for treatment periods in the region of 20 minutes. Again, US medium is used for efficient sound transfer to deeper tissues.
Due to the low intensity linked to the 1:4 pulsing there is little, if any, thermal effect although Welgus et al. (1981) found that some enzymes such as collagenase are sensitive to temperature changes of less than 1°C.

Much of the original research on LIPUS was carried out on the effects on bone healing and this modality was approved by the FDA in the United States in 1994 for the accelerated healing of fresh fractures and then approved by the same body in 2000 for the treatment of established non-union fractures. The studies presented to the FDA demonstrated that LIPUS had a positive effect during all three main stages of fracture healing, i.e. inflammatory, reparative and remodelling by enhancing angiogenesis, chondrogenesis and osteogenesis.

**LIPUS effects on bone**

The original work on fractures in the 1950’s involved therapeutic doses of US with minimally favourable results shown by Buchtala and Maintz but they also found that reduced callus formation was noted on treatment at intensities of 1 – 2.5 mW/cm². Further research by De Nunno and Corradi and Cozzolino showed mixed results at therapeutic levels of intensity and original work involving decreasing intensity levels and pulsing the output by Duarte in 1983 showed uniformly good results that led to the development and use of the first LIPUS machines.

<table>
<thead>
<tr>
<th>Target lesion</th>
<th>No of patients analysed</th>
<th>% reduction in healing time (95% CI)</th>
<th>% reduction in healing time (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conservatively managed fresh fractures</td>
<td>67</td>
<td>46.3 (33.8 to 56.5)</td>
<td>33.8 (19.0 to 45.8)</td>
</tr>
<tr>
<td>Kristiansen et al 1997</td>
<td>61</td>
<td>30.3 (14.7 to 43.1)</td>
<td></td>
</tr>
<tr>
<td>Mayr et al 2000</td>
<td>30</td>
<td></td>
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<tr>
<td>Pooled estimate (n=158), $I^2 = 41.6%$</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Operatively managed fresh fractures</td>
<td>32</td>
<td>-24.0 (-71.9 to 0.6)</td>
<td>42.5 (31.7 to 51.6)</td>
</tr>
<tr>
<td>Emami et al 1997</td>
<td>30</td>
<td></td>
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<tr>
<td>Leung et al 2004</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled estimate (n=62), $I^2 = 90.0%$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operatively managed non-union</td>
<td>21</td>
<td>40.4 (30.8 to 48.7)</td>
<td></td>
</tr>
<tr>
<td>Overall pooled estimate (n=24.1), $I^2 = 76.9%$</td>
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</table>
cycle. Dyson and Suckling\textsuperscript{12} postulated that these cavities can act as concentrators of acoustic energy resulting in shearing and micro-streaming fields and the same authors described acoustic streaming as "a small scale eddying of fluids near a vibrating structure such as cell membranes and the surface of a stable cavitation gas bubble" which many authors, including Rawool et al\textsuperscript{13} have suggested may have a direct effect on cell membrane permeability and these changes in cell membrane permeability may result in an increase in micro-mechanical blood pressure leading to accelerated fracture healing.

Cavitation remains, however, a plausible theory but has never been adequately confirmed in tissues. Other studies have suggested that LIPUS may induce micro-motion and produce mechanical stimulation and so follow Wolff’s Law\textsuperscript{14} which basically states that bone remodels in response to the mechanical stresses to which it is subjected.

Gross et al\textsuperscript{15} and Rubin et al\textsuperscript{16} have suggested that as LIPUS energy is absorbed at a rate proportional to the tissue density, gradients of mechanical stress would be produced when applied to a healing callus where cartilage / bone / collagen interfaces abound.

LIPUS has been shown to be less effective in tissues where there are no gradients in tissue density such as intact bone (Warden et al\textsuperscript{201}) and patellar tendinopathies (Warden et al\textsuperscript{208}).

Further evidence of the effectiveness of LIPUS in the accelerated healing of fractures comes from a double-blind trial by Heckman et al\textsuperscript{19} which showed clinical healing time of Grade 1 open tibial fractures was around 86 days in the LIPUS group opposed to around 114 days in the control group (P < 0.01) and radiographic healing time was around 96 days in the LIPUS group as opposed to around 154 days in the control group (P<0.0001). Heckman’s results and conclusions were reinforced in 2000 by a prospective randomised clinical trial on scaphoid fractures by Mayr et al\textsuperscript{20}. They found healing of the fractures in 43.2 +/- 10.9 days in the LIPUS treated patients against 62 +/- 19.2 days in the control group (P<0.01). Trabecular bridging six weeks after injury showed 81.2% +/- 10.4% healed in the LIPUS group against 54.6 +/- 29% in the control group (P<0.05). It is well accepted that the scaphoid has a greater tendency to progress to delayed and non-union than most other fractures and so these results could point the way to a new attitude towards management of fresh scaphoid fractures to try to prevent the complications that the poor vascularity of scaphoid presents to the orthopaedic world.

It has been well established that there is a marked increase in angiogenesis in fractures treated with LIPUS, probably due to up-regulation of vascular endothelial growth factor with the last study in Feb 2011 by Cheung et al\textsuperscript{21}. This study, most interestingly, was done on osteoporotic bone and concluded that LIPUS can accelerate osteoporotic fracture healing by enhancing callus formation, angiogenesis and callus re-modelling. As fractures in osteoporotic bones in the elderly can, at present lead to considerable expenditure in long term care and outpatient care, any intervention proven to accelerate the rate and incidence of full fracture healing should be welcomed by the orthopaedic world. A study published in 2007 by Burge et al\textsuperscript{22} showed that the cost of osteoporosis related fractures to the USA in 2005 was $17 billion, with a projected 50% increase by 2025. 30% of this total was long term care and 13% was outpatient care.

If LIPUS continues to show in further trials to be effective in accelerating the healing of osteoporosis related fractures, the orthopaedic world could witness a reduction in costs to the state and, more importantly a reduction in the numbers of those patients who progress from out-patient care to long term care who, in the process lose their ability to perform activities of daily living and consequently their independence.

It is important to remember that LIPUS appears to have no effect on intact bone (Warden et al\textsuperscript{207}) so cannot be used to help prevent fractures in osteoporotic patients. This is most likely due to the lack of tissue density gradients which have been shown to be the optimal site for LIPUS effectiveness.

World-wide clinical studies using LIPUS for treatment on non-unions in a self-paired control study demonstrated a healing rate of 88% in those with an average of 23 months since fracture. When compared with surgery LIPUS treatment in non-unions has shown the same success rate and this fact presents an effective argument to orthopaedic surgeons to delay potentially dangerous, expensive and painful surgery in favour of a non-invasive, cheaper, painless and apparently equally effective option of LIPUS.
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LIPUS effects on soft tissues

Following the acceptance in the 1990’s by the FDA of LIPUS for the treatment of all stages of bone fracture, there has been extensive research into the effects of LIPUS on various types of soft tissue. Although some of the research has been on tissues which would appear to have little relevance from a therapeutic point of view, many of these studies have demonstrated the mechanism by which LIPUS has its action at a cellular level and so have given an insight into the practical application of LIPUS.

Nucleus pulposus

Hiyama et al (2007)\textsuperscript{23} conducted a study to assess the synergistic effects of LIPUS and transforming growth factor-\(\alpha\) (TGF-\(\alpha\)) receptor genes on nucleus pulposus cells. This followed on from a study by the same group demonstrating that LIPUS increased the capacity of human intervertebral nucleus pulposus cells to synthesise proteoglycan (PG). They demonstrated that although there was no increase in cell proliferation, there was an increase in PG synthesis and TGF-\(\alpha\) production and went on to suggest that LIPUS would be a promising new therapy for prevention of inter-vertebral disc degeneration which is said to be one of the primary causes of LBP.

Omi et al (2008)\textsuperscript{24} noted a doubling of tissue inhibitor of metallo-proteinase-1 (a type of protease that degrades extra-cellular matrix proteins) as well as a doubling of local monocyte chemotaxis protein-1 in LIPUS treated tissue when compared to control. Similar results were found by Iwabuchi\textsuperscript{25} et al leading to the suggestion that LIPUS-induced macrophage migration may play an important role in intervertebral disc (IVD) remodelling and possibly IVD hernia regression. This study went on to propose that macrophages could enter the IVD following the increase in capillary blood flow and in the cell-membrane permeability caused by LIPUS stimulation.

Further studies by Miyamoto et al\textsuperscript{26} demonstrated a 16-19\% (P<0.05-0.0001) increase in collagen synthesis by cells isolated from the IVD and exposed to LIPUS and went on to suggest that LIPUS may prove useful for tissue engineering of IVD tissue in future.

It is important to note that these studies on LIPUS treatment for IVD lesions were performed on in vitro specimens and although the efficacy has been demonstrated in vitro it would appear difficult if not impossible to enable a practical in vivo mode of application.

Ligaments

In studies comparing the effects of LIPUS with NSAID’s relating to ligament healing the conclusion was that LIPUS accelerated the process while NSAID’s delayed it, the extent of the healing was, however much the same. When used in combination the benefits of LIPUS were not counteracted by the detrimental effect of the NSAID’s suggesting that the LIPUS effect was not via the cyclo-oxygenase-2 / prostaglandin E2 pathway\textsuperscript{27, 28}.

A study by Takakura et al\textsuperscript{29} showed that after 12 days the LIPUS treated MCL’s of rats showed significantly superior mechanical properties in ultimate load, stiffness and energy absorption when compared with control (P<0.05). It concluded that LIPUS is effective for the enhancement of MCL injuries. In 2005 Sparrow et al\textsuperscript{30} carried out a controlled laboratory study in which they tested the effect of LIPUS on the healing of transected MCL’s of rabbits with the ligaments being evaluated biomechanically after 3 or 6 weeks and assayed for collagen concentration and relative collagen types I and II proportions. The conclusion was that LIPUS increased the proportion of collagen type I, hence improving some structural properties, as well as modestly increasing scar cross-sectional area. They considered that LIPUS treatment after ligament injury may facilitate earlier return to activities and decrease the risk of re-injury.

Tendons

The main studies on the effectiveness of LIPUS on tendon problems tend to be divided into 3 sub-categories:

1. Tendinopathy.
2. Tendon ruptures.
3. Tendon-bone junction injuries (TBJ).

Tendinopathy: as previously mentioned Warden et al\textsuperscript{18} in 2008 conducted a randomised, double-blind, placebo-controlled study on clinically confirmed patellar tendinopathy in adult human volunteers during which the LIPUS was self-applied for 20 mins per day, 7 days per week for 12 weeks. The conclusion was that LIPUS was no more effective than placebo in the management of symptoms.
D’Vaz et al (2005) experienced a similar result in their double-blind randomised, controlled trial of the effectiveness of LIPUS on patients with at least a 6 week history of lateral epicondylitis – a tendinopathy of the common extensor tendon. These results should not however be surprising since, as has been previously suggested, for LIPUS to be effective the existence of a tissue density gradient appears to be a pre-requisite and there would be no reason for such gradients to present in cases of tendinopathy.

Tendon ruptures: Enwemeka et al (2010) began work on tendon healing with LIPUS in 1990. They tenotomised and repaired rabbit TAs and applied LIPUS to half of them and placebo applied to the remainder. They used 0.5mW/cm² for 5 mins daily for nine days after which they excised and tested the tendons. The LIPUS treated tendons were found to show a significant increase in tensile strength (p<0.02), tensile stress (p<0.005) and energy absorption capacity (p<0.001). They concluded that LIPUS may enhance the healing process of surgically repaired TAs.

Sai-Chuen Fu et al (2010) carried out an in vivo study on tenotomised rat patellar tendons and found that there was a positive improvement in collagen synthesis when LIPUS was applied on the 4th or 14th day post-op (single application) but not when applied on the 28th day. They concluded that LIPUS should be applied during the granulation phase of tendon healing but not during the remodelling phase.

Tendon-bone junction injuries: In 2007 Walsh et al conducted a study in which a single digital extensor tendon auto graft was inserted into bony tunnels in the tibia and femur of sheep whose ACLs had been excised.

Fixation was by an endo-button and bony post and in the LIPUS group it was applied daily for 20mins over the femoral and tibial tunnels. The results showed that the LIPUS group had increased cellular activity at the TJ, increased tendon-bone integration, enhanced vascularity and the peak load and stiffness were greater (p<0.05) than control. They concluded that these factors had a clinical relevance and indicated that LIPUS may be used to enhance ACL reconstruction healing at the tendon-bone junction.

Similar studies have been performed by Hongbin Lu et al, Qin et al and Papatheodorou et al.
Once again, the existence of tissue density gradients abound at healing tendon-bone interfaces and the effectiveness of LIPUS at such sites could have been predicted.

Application

As the area of the average LIPUS transducer is only about 4cm² it is essential that very accurate surface marking of the exact site of the injury be performed prior to commencing treatment to ensure that the LIPUS output is exactly penetrating the injury. In the case of delayed union oblique fractures where there are signs of failure to heal over only a segment of the fracture, obtaining sight of the X-rays would be vital in order to place the transducer accurately at the correct point and at the correct angle.

1. Measure the length of the fractured bone on X-ray and the distance between fracture point to be treated and where the bone ends (Figure 2).
2. Measure the actual bone length and compare with the X-ray measurement (Figure 3).
3. Mark the site to be treated (Figure 4).

Most studies suggest that LIPUS appears to be most effective in the early stage of healing of soft tissue although it appears to be effective at all stages of bony healing.

Conclusion

Although LIPUS is part of the US family its application in no way copies the actions of therapeutic US. Whereas it is unlikely that any responsible physiotherapist would consider applying therapeutic US to sutured TAs in the very early post-operative stage, studies have shown that this is precisely the most beneficial time for LIPUS to stimulate repair.

Likewise, any application of therapeutic US to fractures would normally be considered to be contra-indicated, indeed studies show therapeutic US to often cause bone reabsorption. LIPUS, however, has been shown to be beneficial at all stages of fracture healing, even very early stages when, in problem fractures such as scaphoid the potential for non-union may be reduced.

The change in thought process towards early intervention is reinforced by studies demonstrating LIPUS improves TBJ strength in tendon / ligament grafts such as ACL repair and MCL repair.
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With LI-PU-S being shown to be effective in applications which have hitherto not been considered the realm of the physiotherapist, i.e. treatment, early TA repair and early ACL and MCL repair, perhaps physiotherapy as a profession and/or physiotherapists as individuals might then consider working to educate orthopaedic surgeons to change their thought processes away from using physiotherapy only at the rehabilitation stage of such conditions and rather towards early intervention to accelerate repair, reduce periods and levels of morbidity, help prevent complications such as non-union and shorten the period to full recovery.

References

26. Miyamoto K et al 2005 Exposure to pulsed low-intensity ultrasound stimulates extracellular matrix metabolism of bovine intervertebral disc cells cultivated in alginate beads. Spine 30:2398-2405

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