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Therapeutic Ultrasound: Finding the Sweet Spot for Bioburden Control and Wound Healing

Teresa A. Conner-Kerr*

Department of Physical Therapy, School of Health Sciences, Winston-Salem State University

Clinically, therapeutic ultrasound has been used by rehabilitation experts in physical therapy and other fields for more than 60 years [1]. Therapeutic indications have included a wide range of conditions (acute and chronic inflammation, tissue healing and repair, scar management, pain modulation and bone healing). Over the past six decades, high frequency ultrasound in the 1-3.3 MHz (1,000,000 to greater than 3,000,000 cycles per second) range has been primarily used in treating these conditions. However, in the past decade, we have seen the introduction of low frequency ultrasound for the management of nonhealing, recalcitrant wounds. Low frequency ultrasound (LFU) generators (<100,000 and > 20,000 hertz) are used for debridement [2], bioburden control [3] and to stimulate wound healing [4] through both non-contact and jet-spray modes of delivery.

A review of the research examining the effects of LFU, demonstrates an evolving body of evidence to suggest a sweet spot in the frequency range for killing wound pathogens, enhancing antibiotic effectiveness and stimulating human cells. Work by a number of investigators has demonstrated the effectiveness of 25-35 kHz LFU in killing common wound pathogens [3,5,6] as well as antibiotic resistant species [3,6]. Thirty five kHz LFU also appeared to re-sensitize Methicillin-resistant *Staphylococcus aureus* to methicillin *in vitro* [3]. Similarly, other work has demonstrated that LFU in higher frequency ranges (67 kHz) enhances the effectiveness of antibiotics when bacteria are treated with the two modalities (antibiotic and LFU in combination) [7]. However, at this higher frequency, LFU does not directly kill bacteria. Interesting in the intermediate range of 40 kHz, an average reduction of 33% of bacteria was seen after 5 minutes of treatment with LFU *in vitro* compared to 99.99% with 180 seconds using 35 kHz [8]. Forty kHz LFU treatment also increased the number of Methicillin-resistant *Staphylococcus aureus in vitro*. This finding was not observed with frequencies at or below 35 kHz.

When reviewing the literature, there are reports across both 35 and 40 kHz frequencies in regards to mammalian cell stimulation. Conner-Kerr demonstrated a positive effect on a human neuronal monolayer development *in vitro* along with enhanced fibroblast migration rates *in vitro* for both 35 and 40 kHz [3,9,10]. As mentioned previously, human clinical trials have also demonstrated increased healing rates with LFU at the 40 kHz frequency [4]. Taken together, the evolving literature appears to indicate that there is a potential sweet spot for achieving both microbial control and cellular stimulation for wound healing and this sweet spot appears to be 35 kHz. Much research is yet to be done, however, the picture that is emerging points to select frequencies for achieving both bioburden control as well as wound healing. This sweet spot may be 35 kHz. Frequencies above 35 kHz do not appear to be as effective at bacterial killing. However, research demonstrates consistently positive results in facilitating wound healing. Reversal of antibiotic resistance has not been demonstrated at any frequency other than 35 kHz. Antibiotic effectiveness has been enhanced at 67 kHz without the concomitant effect of direct bacterial killing.

The above research has shifted the treatment paradigm for physical therapist and others who employee ultrasound to enhance healing. Practice has moved away from high frequency ultrasound to units that are based on low frequencies. The degree of debridement appears to be governed by the acoustic energy delivery method with the lower frequencies (35 kHz and below) used primarily in debridement. As the technology evolves, as well as our understanding of the mechanisms that underlies treatment effects, we will likely find that the clinical utility of LFU will expand.

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***Corresponding author:** Teresa A. Conner-Kerr, Department of Physical Therapy, School of Health Sciences, Winston-Salem State University, USA, Tel: (336) 750-2193; E-mail: connerkerrt@wssu.edu

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