Meeting report

MIST ultrasound therapy: the science and the benefits

This report focuses on the plenary session held at Wounds UK Harrogate, 2010 presented by Professor Keith Cutting, Pam Unger; Tissue Viability Nurse Specialist Ray Norris and Dr Vickie Driver.

The event was chaired by Professor Keith Cutting, Visiting Professor of Buckinghamshire University who opened the session by raising the challenges of introducing a new technology in wound care. He stated that sceptics tend to question whether new technologies have anything to offer that has not been seen before. New products need to have an evidence base that quantifies improvements, as well as reducing costs.

The focus of the plenary session, he added, was to show clinical and robust randomised controlled trial (RCT) evidence to support the use of an innovative, low frequency, non-contact ultrasound wound treatment device, the MIST Therapy System (Celleration Inc) to treat chronic and hard-to-heal wounds.

Science and benefits of MIST Therapy

Pam Unger; Vice President of Clinical Research and Reimbursement at Celleration, first spoke about the science and benefits of MIST Therapy.

She explained to the audience exactly what ultrasound was, likening it to speaking to the audience. The soundwaves coming from the voice bounce off the listener’s eardrums causing a vibration, thereby enabling the listener to hear what is being said. However, if that vibration is converted to electrical energy, it becomes a vibration or a mechanical pressure wave with a frequency greater than the upper limit of human hearing. This is why when the ultrasound device is turned on, essentially nothing is heard. However, the generated pressure wave moves through a coupling medium (e.g. air, water, gel, mist) causing the molecules of the medium to vibrate. It is these vibrations that deliver the therapeutic effects of ultrasound to the tissues.

How is ultrasound created?

Pam Unger went on to explain how ultrasound is produced. An electrical generator creates an electrical output with a specified low frequency (40kHz). The transducer converts the electrical input from the generator into mechanical energy. The resulting pressure wave is transmitted to the bed of the wound, via the coupling medium.

How is ultrasound delivered to the body?

Pam Unger then described the various ways in which ultrasound can be delivered to the tissues. In the US, ultrasound tubes are available, where the body or body part is submerged in a tank and exposed to ultrasound energy. In some cases, a thin layer of coupling agent (gel medium) is used to limit the impedance. Alternatively, the ultrasound transducer may make direct contact with the skin, as is the case with the low frequency ultrasound devices that are available for debridement. These touch and scrape the surface of the wound in a manner similar to that of a blade or curette.

Pam Unger then introduced MIST Therapy, a low frequency (40kHz), low intensity, non-contact ultrasound therapy that is delivered to the wound bed and the underlying tissues with a gentle saline mist that is generated from saline dropping in front of the transducer (Figure 1). The mist of saline propelled by the ultrasound waves bathes and cleanses the wound. This painless, non-contact, non-thermal energy delivery results in four effects that are beneficial to wound healing, namely:

- Active cell stimulation
- Increased blood flow
- Decreased bioburden
- Cleansing and gentle debridement.

Benefits of low frequency ultrasound therapy

One of the most beneficial aspects is the reduction of bacteria in the wound bed (Niezgoda and Schulze, 2003; Pierson et al, 2005). Energy penetrates 3-3.5mm below the surface of the wound killing bacteria present. As a result of the removal of bacteria from the wound bed, there is a significant reduction in exudate. There is also evidence to show increased blood flow and micro-circulation. MIST also assists with cleansing and debridement. There is no immediate removal of necrotic tissue or fibrinous slough, this is performed by gentle maintenance debridement.

Active cell stimulation is achieved by creating a minimal stretch on the healthy cells, thereby allowing the wound to proceed through the normal healing process.

Pam Unger showed a video of the therapy being performed, and highlighted how the mist could barely be seen while therapy was being delivered (Figure 1). She described how the saline bottle should be moved, 0.5-1.5cm away, in a serpentine fashion over the bed.

Figure 1. Saline mist bridging the gap between the ultrasound and the wound bed.
of the wound for about five minutes, depending on the size of the wound approximately three times a week.

In the US, MIST Therapy has a Food and Drug Administration (FDA) indication to promote wound healing. Pam Unger commented that there were two randomised controlled trials (RCTs), one prospective trial and five retrospective trials which encompass over 500 patients treated with MIST Therapy. Over 200 patients were in the control groups, as well as two observational registries, 10 case series, and multiple patient case studies that have been presented in posters. The collected data suggest that an 85% reduction in wound size is seen in eight weeks of MIST treatment, together with a 79% reduction in pain.

References

MIST ultrasound therapy in wound healing: a case report
Ray Norris, Clinical Nurse Specialist in South-West Essex community services continued the session by describing the management of a patient with a recalcitrant leg ulcer using MIST Therapy.

The patient presented was a 63-year-old gentleman with a five-year history of ulceration, following trauma injury. Previous treatment had involved dressings and compression therapy. However, he was unable to tolerate adequate levels of compression, so had been receiving suboptimal treatment for some time.

Apart from analgesia, warfarin was the only medication taken by the patient. He had a previous history in the ulcerated limb of three deep vein thromboses (DVTs), but no other history that would prevent healing.

Ankle brachial pressure index (ABPI) results for both the left and right legs and the findings of ultrasound sonography, indicated that no arterial disease was present. The ulcer was venous in origin, and in the absence of any other contributing factors, would usually be expected to go on to heal uneventfully. However, it had become a significant impairment to the patient’s life. At 63 years’ old, he was still working as a mechanic and was a member of a golf club, but for the past few years had found such activities difficult. Pain associated with the wound registered as 8 on a visual analogue scale (VAS) (where 0 = least pain and 10 = most pain), and this was having a considerable impact on quality of life.

Despite the use of opioid analgesia, the patient’s pain was not controlled adequately. He had repeated episodes of infection and a score of 19 on a dermatology life quality index (DLQI). This index highlights the impact of a chronic wound on quality of life. A score above 10 indicates significant impact for that individual.

The patient was identified by South-West Essex community services as being suitable for treatment with MIST Therapy. Figure 2 shows the extent of the ulceration on day 0.

Ray Norris pointed out that from the clinic’s experience of using MIST Therapy, an almost immediate response is achieved. On day 2 (Figure 3) there was a reduction in the patient’s pain score to 5 (VAS). However, this result may have a psychological or placebo element to it, as patients feel they will receive a therapy that could work after a long period of seeing no improvement. The patient’s DLQI also reduced, and a noticeable improvement was seen in the wound bed.

By day 17 (Figure 4), after only eight treatments, the wound bed was progressing to healing. This continued (Figures 5–6) and after one month the wound had reduced in size, which had a positive impact on the patient’s quality of life.

Figure 6 shows the lateral aspect of the ulcerated limb after 18 treatments.
Ray Norris emphasised that from the clinic’s experience, wounds reach a stage with MIST Therapy where they ‘take off’. At this point, the therapy is discontinued and the wound continues on its healing trajectory.

Following 77 days of MIST Therapy the patient had only a small wound remaining, which was expected to progress to healing and was treated with a hydrocolloid dressing and compression hosiery, which he was now able to tolerate.

By day 77, the wound was approaching healing (Figure 7). Ray Norris emphasised that from the clinic’s experience, wounds reach a stage with MIST Therapy where they ‘take off’. At this point, the therapy is discontinued and the wound continues on its healing trajectory.

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The role of critical colonisation in delayed healing is also a subject of much debate. Such discussion has moved clinicians on to thinking about biofilms as primitive, single-cell creatures. The Symposium on Advanced Wound Care (SAWC) in Florida in 2003 brought this to focus: that wounds have biofilm and that these biofilms could differentiate, communicate, cooperate, and deploy collective defences against antibiotics. Biofilms self-create the glycocalyx that can ward off bacteria, be it Escherichia coli, Streptococcus, Staphylococcus, or meticillin-resistant *Staphylococcus aureus*, which are common in devitalised tissue.

Biofilms are formed in the presence of chronic bacterial colonisation or infection and are prevalent on moist surfaces. They are essentially complex communities of bacteria that primarily consist of an extracellular polysaccharide matrix or glyocalyx in which the microorganisms are embedded. These biofilms can exist in any nutrient-sufficient system. Bacterial biofilm infections are especially problematic because they are resistant to host immune responses and markedly more resistant to antibiotics and topical bactericidals. Biofilms formed from mixed bacterial species are thought to enhance the virulence of each other synergistically. Reports indicate that biofilm cells can be at least 500 times more resistant to antibacterial agents.

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The formation of biofilms is common in devitalised tissue and on infected medical devices such as endotracheal tubes, Hickman catheters, central venous catheters, contact lenses, and orthopaedic devices. They can be adherent to surfaces and difficult to dislodge.

**Why do we care about bacteria in wounds?**

Dr Driver made the point that whereas once we used to think in terms of preventing bacteria in wounds, with the clinical spectrum of wound colonisation and infection leading to septicaemia (Edwards and Harding, 2004), it is death, limb loss, and osteomyelitis that are actually being prevented. It is not just about treating the wound, but preventing patients from getting very sick by stopping the problems that can arise with acute and chronic wounds.

One new treatment option that addresses debridement and biofilm disruption is ultrasound. This acoustic pressure wound therapy can be high or low in intensity (Table 1). There are two systems available, contact and non-contact. Table 2 itemises the contact and non-contact ultrasound therapy systems currently available. Unfortunately, there is little literature to support the former; however, the non-contact system discussed in this session, MIST Therapy, has a growing body of literature behind it.

### Table 1

<table>
<thead>
<tr>
<th>Acoustic pressure wound therapy</th>
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<tbody>
<tr>
<td><strong>Ultrasound pressure</strong></td>
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<tr>
<td>kHz high frequency</td>
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<td>kHz low frequency</td>
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**Method of wound debridement currently in use include:**

- Autolytic
- Mechanical
- Maggot therapy
- Surgical/sharp
- Enzymatic
- Hydrotherapy
- Ultrasound.

It is also important to address other factors that may delay wound healing. The degradation of growth factors also poses a problem, as there are uncontrolled matrix metalloproteinases (MMPs) that prevent wounds from healing. MMP activity levels are higher in the older patient, predisposing the elderly to tissue breakdown, as well as creating a hostile environment for healing (Ashcroft et al, 1997).
Ultrasound devices exert their effect on the healing process by modulating biological steps in the inflammatory phase, leading to a higher quality wound bed.

Another evidence-based advanced wound care therapy is negative pressure wound therapy (NPWT). Dr Driver said that she was frequently asked if NPWT could work together with ultrasound, and explained that both therapies can be used together to generate an even more comprehensive solution to wound healing. It is important to think about the variety of therapies available and find the best course of treatment for the patient and their wound.

Hoover et al (2002), in experiments at Penn State and Ultran Labs, Boalsburg, Pa, showed that ultrasound can kill bacterial spores, which are far more resistant to other treatments. Celleration has a growing body of research to support the significant clinical contribution that MIST Therapy can make to tissue repair. Its proven clinical effects include:

- Decreased oedema
- Triggered mast-cell degradation
- Increased blood flow
- Increased oxygen delivery
- Increased delivery of macrophages
- Stimulation of collagen deposition
- Stimulation collagen remodelling
- Bactericidal effect (Byl et al, 1992; Suchkova et al, 2002).

Ultrasound is not just a therapy that can heal a wound, but it has an accompanying history and science, she commented, which is a rare occurrence in the field of wound care.

MIST Therapy addresses five of these factors by:

- Stimulating angiogenesis in the wound, creating a new blood supply and a better circulation for healing
- Stimulating cells in the wound to actively produce growth factors required for healing
- ‘Waking up’ senescent cells by activating key cellular pathways
- Decreasing inflammation by interfering with key molecular steps in the inflammatory process
- Addressing bacterial infection — the ultrasound energy destroys bacterial cell walls and helps to remove the biofilm coating wounds (Torke, 2004; Breuing, 2005).

Ultrasound therapy and debridement devices

<table>
<thead>
<tr>
<th>Ultrasonic treatment and cleanser</th>
<th>Modality</th>
<th>Manufacturer</th>
</tr>
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<tbody>
<tr>
<td>MIST™ Therapy (Celleration Inc)</td>
<td>Ultrasonic treatment and cleanser</td>
<td>MIST™ (Celleration Inc)</td>
</tr>
<tr>
<td>Misonix® (Misonix Inc)</td>
<td>Ultrasonic scalpel, cleanser and treatment</td>
<td>Misonix® (Misonix Inc)</td>
</tr>
<tr>
<td>Sonocure® (Soring)</td>
<td></td>
<td>Sonocure® (Soring)</td>
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<tr>
<td>Quotic Wound Therapy System® (Aorbella)</td>
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<tr>
<td>Hydrosurgery, scalpel, cleanser and suction</td>
<td>Hydrosurgery, scalpel, cleanser and suction</td>
<td>Hydrosurgery, scalpel, cleanser and suction</td>
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<tr>
<td>Versajet® (Smith &amp; Nephew)</td>
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<td>Versajet® (Smith &amp; Nephew)</td>
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The normal wound healing cascade moves quickly. However, the factors that impair healing can take years to overcome, including:

- Impaired angiogenesis
- Deficient growth factors
- Senescent cells
- Sustained inflammation
- Excessive proteolysis

Bacterial infection
- Moisture imbalance
- Physical pressure
- Compromised patient status.

MIST Therapy is a painless, bioactive therapy that promotes healing through cell stimulation while reducing bacterial load. Figure 8 shows the results that can be achieved with this method of debridement which helps to loosen tissue.

The right-hand figure shows the wounds after ultrasound debridement in the clinic. Ultrasound debridement and NPWT were continued in the operating theatre with the patient only losing the end of the second digit.
smaller than the bacteria present in wounds. In the experiments, bacterial spores contained in a paper envelope were placed slightly (3mm) above the active area of a specially equipped source of inaudible, high frequency (70–200kHz) sound waves and hit for 30 seconds. There was no contact medium, such as water or gel between the ultrasound source and the spores, as is typically used in low-power medical diagnostic ultrasound. The high-power ultrasound, currently used for cell disruption, particle size reduction, welding and vaporisation, was shown to be 99.99% effective in killing bacterial spores after only 30 seconds of non-contact exposure. The experiments mark the first time that non-contact ultrasound has been shown to inactivate bacterial spores.

The researchers stated that the experiments demonstrate that non-contact ultrasound is a potentially safe, effective, non-radioactive way to decontaminate mail, including packages, since ultrasound waves can potentially penetrate cardboard and other wrappings, just as they do layers of skin and tissue when used to image internal organs in the human body. They added that the technology could sterilise medical and surgical equipment, food materials, air duct systems of buildings, airplanes and even space stations.

An RCT looking at diabetic foot ulcers was undertaken in Chicago by Ennis et al (1995), where 40.7% of the patients in the MIST Therapy group (p=0.036) achieved complete wound closure at 12 weeks, compared with 14.3% in the control group. Seven peer-reviewed studies have been published (Thawer and Houghton, 2004; Ennis et al, 2005; Gehling and Samies, 2007; Kavros and Schenck, 2007; Kavros et al, 2007; Lai and Pittelkow, 2007), five clinical studies, and two RCTs, all demonstrating statistical significance. She concluded that it is not just NPWT that comes with supportive literature, but also MIST Therapy.

Dr Driver referred to a prospective study recently undertaken by her institution, the results of which will be published shortly. Three groups of four patients with diabetes were randomly selected. Over four weeks their wound healing was followed, with weekly biopsies and fluid examination. Cells, growth factors, cytokines and bioburden were also analysed using multiplexed ELISA assay.

Figures 9–12 show the change in wound areas for some patients from this case series in just four weeks. Dr Driver stressed how she did not expect such a positive change in such a short period of time.

Figure 13 shows the change in wound area with MIST Therapy over the
The dark blue line (group 1) shows the healing rate of the group who were treated three times a week, as clinically indicated in the literature. Analysis of the cells has yet to be done.

Dr Driver concluded by turning to cost-effectiveness, which has also been addressed in their study (Driver et al, in progress). Margolis’s work on DFUs was compared with the RCT by Ennis. It was found that 91% of patients healed with ultrasound or progressed towards healing in 12 weeks, compared with 70% for standard care. Ultrasound is not cheaper than other advanced therapies, she stated, but due to the faster healing times than with standard care, there is a saving. The results show a little over $2 million of savings for every 1,000 patients treated for 12 weeks. The data is not completely analysed as yet, but is currently pointing towards cost-effective care.

Figure 13. Changes in wound area after MIST Therapy over the study period.

<table>
<thead>
<tr>
<th>Area</th>
<th>1W</th>
<th>2W</th>
<th>3W</th>
<th>4W</th>
<th>5W</th>
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<tbody>
<tr>
<td>Group 1</td>
<td>1.72</td>
<td>1.44</td>
<td>0.38</td>
<td>0.33</td>
<td>0.39</td>
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<tr>
<td>Group 2</td>
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<td>2.41</td>
<td>2.11</td>
<td>2.09</td>
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<tr>
<td>Group 3</td>
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<td>0.77</td>
<td>1.49</td>
<td>1.79</td>
<td>1.35</td>
</tr>
</tbody>
</table>

References
Suchkova VN, Baggs RB, Sahni SK, Francis CW (2002) Ultrasound improves tissue perfusion in ischemic tissue through nitric oxide dependent mechanism. Thromb Haemost 88: 865–70

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