A Review of Mechanical Adjuncts in Wound Healing: Hydrotherapy, Ultrasound, Negative Pressure Therapy, Hyperbaric Oxygen and Electrostimulation

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Introduction

The process of normal wound healing involves a carefully regulated sequence of cellular activity. These activities provide the foundation for the mechanisms of wound repair including: extracellular matrix synthesis, angiogenesis, wound contraction and epithelialization. These mechanisms occur to different degrees during the four types of healing. Primary healing occurs when a wound is closed within hours of its creation. Delayed primary healing occurs when the wound is purposefully left open, for some interval, prior to closure. Healing by secondary intention occurs in wounds that are left to heal with or without topical therapy. Here, dressing changes are performed until the wound closes by contraction and epithelialization. Finally, partial thickness wounds or wounds involving the epidermis and part of the dermis heal by epithelialization.[1]

Chronic or non-healing wounds may develop in the setting of many diseases and are the source of considerable morbidity as well as health costs. These problem wounds can develop after trauma, infection, cancer, radiation therapy, frostbite, animal bites, and immobility. They become more complex when the patient suffers from diabetes mellitus, peripheral vascular disease, autoimmune disease, neuropathy, steroid dependence or venous stasis. Despite considerable laboratory and clinical study no single therapy has proved beneficial for all types of wounds. However, several devices that stimulate wound healing have found constructive, adjunctive niches. They include hydrotherapy, ultrasound, negative pressure therapy, hyperbaric oxygen and electrostimulation.

Normal Wound Healing[1]

Tissue injury results in local vascular injury. The ensuing bleeding floods the wound with mediators of the coagulation cascade. Factors are released to attract platelets to the site of injury. These include mediators such as platelet-derived growth factor and transforming growth factor-beta. Macrophages are attracted to the site of injury by these factors, debride local necrotic tissue and orchestrate the wound healing process by releasing cytokines such as interleukins and other factors. They also stimulate, via these cytokines, fibroblasts to begin collagen production and smooth muscle and endothelial cells to proliferate for angiogenesis. As the collagen matrix and new vessels bridge the wound the surface undergoes epithelialization. These processes continue until contact inhibition causes it to stop. Throughout this healing, and for many months after the wound has closed, collagenase breaks down the newly formed collagen while new collagen is deposited. This balanced process of collagen production and collagen destruction results in wound remodeling.

Nonhealing Wounds

Failure for wounds to heal is the result of four intertwined conditions: hypoxia, infection, edema and metabolic abnormalities. Each factor exists to varying degrees within each wound. Healing wounds require an oxygen tension of 30mmHg for normal cell division.[2] Oxygen increases fibroblast migration and replication, normal collagen production, and leukocyte killing ability. In chronic wounds, diminished circulation and hence hypoxia fails to provide for the increased cellular metabolism and energy requirements. Although collagen is produced, it is of poor tensile strength and has limited vascular ingrowth to support it.[2] Normal bacterial contamination leads to infection because of the diminished ability of leukocytes to kill and because of the increased amount of necrotic tissue which is due to hypoxia, poor vascular ingrowth and the

release of local wound healing inhibitory factors. The inflammatory aspect of wound healing results from cytokines released by macrophages that increase vascular and cellular permeability. As wound edema increases oxygen must diffuse farther from its source. This is especially evident in diseases such as venous stasis in which the venous hypertension leads to pericapillary deposition of fibrin that acts as a diffusion barrier to oxygen and nutrients.[2] Metabolism can also be affected in disease states such as diabetes mellitus. Non-physiologic levels of glucose and insulin can lead to impaired granulocyte chemotaxis and phagocytic function.[3]

Chronic wounds demand an aggressive, multifactorial approach. Repetitive surgical debridement, revascularization, when necessary, antibiotics and dressings form the foundation of therapy.[4] However, once the wound is clean and well vascularized, they still may not progress to healing. Several adjuvant treatment methods have been developed to further stimulate healing. Each of these adjuvant methods targets specific mechanisms of the healing sequence. We will discuss the physiologic rational, pros and cons and myths surrounding each adjunctive therapy.

Hydrotherapy

Hydrotherapy, or whirlpool, is one of the oldest adjuvant therapies still in use today. Although originally used by physical therapists in the treatment of pain it quickly found a place in wound management. Burn patients, in need of extensive debridement, were immersed in the Hubbard tank, a full body whirlpool.[5] This quickly led to the development and institution of smaller extremity tanks. The premise behind whirlpool therapy is that the whirling and agitation of the water, and injected air, removes gross contaminants, toxic debris and dilutes bacterial content.[6] Unfortunately, there are no double-blind, randomized studies that demonstrate this.[7,8]

Although the water circulation rate and the amount of injected air can be varied, the force generated at the wound surface can be greater than the recommended six psi necessary to cleanse healthy granulation tissue.[5] This pressure, in one study, may damage the developing granulation tissue, hinder migrating epidermal cells and cause maceration.[6] Also, in lower extremity therapy it generally requires the limb to be in a dependent position. This has been found to increase venous hypertension and vascular congestion that may be counterproductive, especially in the limbs of patients with venous insufficiency.[9] Another consideration is the risk of bacterial cross contamination between patients using the same tank. This is usually combated with various antibacterial agents that, while being effective at destroying pathogens, may damage new tissue as well.[10,11]

There are beneficial effects as well. Patients with crush injuries, venous stasis, pyoderma gangranosum, arterial insufficiency, animal bites and occasionally diabetes mellitus often are not neuropathic and therefore have very sensitive wounds. This makes dressing changes quite painful and psychologically distressing. The whirlpool allows the dressings to be soaked off slowly and gently. This gives patients a sense of control as they assist in dressing removal and the feeling of progression in the healing process. Secondly the warmth of the water, generally **35.5^{o} to 39^{o}C**, promotes increased circulation to the wound surface. Finally, these tanks provide resistance, and buoyancy in the case of the Hubbard tank, for active physical therapy.[12]

Despite the lack of prolonged trials showing its efficacy, whirlpool therapy continues to be used for lack of a better option. A common protocol is a 20-30 minute session, three to four times per week. Typically, this is only continued for a brief period.

Recently, the use of *pulsed lavage* has begun to replace whirlpool therapy. Pulsed lavage refers to an irrigating solution delivered at a pressure by a powered device. It has long been appreciated that irrigating wounds reduces the bacterial content. This is aptly surmised in the old adage "the solution to pollution is dilution." However, the best method to deliver the irrigant has only recently been determined. In 1994, based on numerous studies, the Agency for Health Care Policy and Research (AHCPR) published guidelines for irrigation pressures.[13] They suggested that pressures ranging from 4-15 pounds per square inch (psi) were sufficient to remove surface pathogens and debris but would not cause wound trauma or lead to bacterial spread. While this is indeed true it fails to establish the most effective irrigation pressure. A review of the literature reveals that irrigation delivered at the wound surface with a pressure of 10-15 psi effectively removes debris, decreases bacterial colonization and prevents clinical infection[14-16] Furthermore, even with pressures as high as 90 psi there is no evidence that bacteria are driven deeper into the wound leading to bacteremia and thus tissue destruction.[17-20]

The use of pulsed lavage irrigation in place of whirlpool therapy is due to a study by Haynes et al where the rate of granulation tissue formation was compared following pulsed lavage or whirlpool. They concluded that the rate of granulation tissue formation was significantly higher in those receiving pulsed lavage than those receiving whirlpool.[21] Although further studies are needed, it appears that pulsed lavage will replace whirlpool for wound cleansing in patients who can tolerate it from a pain perspective.

Ultrasound

The effectiveness of ultrasound (US) as a noninvasive diagnostic tool has led to investigation into its potential benefits for wound healing. Ultrasound results when electrical energy is

converted to sound waves at frequencies above the range of human hearing (>20,000 Hz). These sound waves can then be transferred to tissue, via a hydrated medium, though a treatment applicator. The depth of penetration is dependent on the frequency; the higher the frequency the less tissue penetration.

The therapeutic effects of US are derived from both its thermal and nonthermal properties. At intensities of 1-1.5 Watts/cm^2 the applicator head transmits warmth to the tissue. This is the mode traditionally used in musculoskeletal conditions such as spasm.[5] In wound healing thermal US has been used in the late stages or remodeling phase to improve scar/wound outcome. More recently, the nonthermal effects of US, which are achieved at intensities of <0.3-1W/cm^2, are gaining interest. At these levels US produces two effects, *cavitation* and *streaming*. Cavitation is the formation of gas bubbles and streaming is a unidirectional, steady mechanical force. These effects cause changes in cell membrane permeability and thus the diffusion of cellular metabolites.[5,22,23]

Many laboratory-based studies have been undertaken to understand the effects of ultrasound on wound healing. To date its effects include cellular recruitment, collagen synthesis, increased collagen tensile strength, angiogenesis, wound contraction, fibroblast and macrophage stimulation, fibrinolysis, and reduction of the inflammatory phase and promotion of the proliferative phase of healing.[24-34]

Although there appears to be considerable laboratory proof that US leads to faster and/or improved wound healing, the clinical evidence has been less convincing. In the clinical setting US is delivered in a low intensity, high frequency, pulsed mode (2 ms period of sonation followed by 8 ms of rest) lasting approximately five minutes per session.[5] Most studies have

focused on venous stasis wounds and pressure sores. Dyson et al, Callam et al, and Roche and West all demonstrated a significant reduction in venous stasis wound size over time when compared to placebo.[35-37] However, Lundberg et al was unable to demonstrate significant healing over placebo.[38] The results for pressure ulcers has been less promising. Paul et al were able to demonstrate favorable results but McDiarmid et al and ter Riet et al demonstrated equivocal or no significant improvement, respectively, with US therapy.[39-41]

Negative Pressure Therapy

Otherwise known as vacuum-assisted closure (V.A.C.,™ Kinetic Concepts Inc., San Antonio, TX), this therapy is fast becoming a mainstay in chronic wound management. Developed for clinical use at the Bowman Gray School of Medicine, the V.A.C. ™ uses a subatmospheric pressure dressing to convert an open wound to a controlled closed wound. The system uses a medical-grade, open-cell, polyurethane ether foam that is cut to the size and shape of the wound and placed within the wound. The pores range in size from 400-600 μm and are in continuity. This allows for an even pressure displacement across the wound and maximum tissue growth. A noncollapsible evacuation tube with multiple fenestrations is placed within or on the foam and the entire wound is covered with an impermeable dressing. The tube is then attached to a vacuum source and subatmospheric pressure of 100-125mmHg is applied in a continuous or intermittent manner.[42] The dressing is changed every two to three days.

Negative pressure therapy exerts many effects on both the gross and microscopic levels. Initially, the negative pressure is applied in a continuous mode. This removes the interstitial fluid/edema thus decreasing the intercellular diffusion distance and improving wound oxygenation. Additionally, the interstitial pressure is reduced which improves blood flow by

allowing vessels, compressed by the excess pressure, to fully expand. It also removes the chronic interstitial fluid that contains multiple inflammatory mediators that inhibit or suppress healthy tissue formation.[43] Typically after the first 24-72 hours the majority of the edema is removed. At this time the pressure is changed to an intermittent setting. This allows for an increased rate of granulation tissue formation. Morykwas et al demonstrated that with the continuous mode granulation tissue formation was increased over controls by 63.3% ± 26.1%; with the intermittent mode granulation increased 103.4% ± 35.3%.[44] Another significant advantage of the V.A.C. ™ is its ability to reduce bacterial contamination within the wound. In the same study Morykwas et al demonstrated that the V.A.C. ™ reduced bacterial levels to below 10^5 organisms per gram of tissue, the quantity accepted as the clinically infected level, within five days. In contrast, control wounds treated with dressing changes alone, reached this level at 11 days.[44] Finally, another significant advantage for this dressing is its necessity to be changed only every 48-72 hours. This allows for improved patient comfort, less time spent changing dressings and a cleaner, more hygienic dressing.

Few complications have been associated with the V.A.C. ™. Pressure necrosis of skin under the evacuation tubing is uncommon but increases if placed over a bony prominence or in an ischemic wound. Unfortunately, the dressings can be quite adherent to the wound bed resulting in discomfort upon removal in the non-neuropathic patient. This can be alleviated by placing a Teflon® or Silastic® perforated sheet between the wound bed and sponge dressing. These patients may also experience initial discomfort with the negative pressure; this usually dissipates within 20 minutes. If not relieved, a small reduction in pressure frequently solves the problem.

Granulation growth into the sponge may occur between dressing changes resulting in minor bleeding at dressing change. Rarely is cautery necessary to control the bleeding.

Due to the success of the V.A.C. ™ in chronic wounds, it is now being used in a multitude of clinical settings: as a temporary abdominal closure, degloving injuries, poststernotomy mediastinitis, acute traumatic wounds, subacute wounds, bones with exposed hardware, osteomyelitis and as a skin graft bolster.[45-50] The negative pressure dressing is a great temporizer. It allows the reconstructive surgeon to effectively plan for surgery when the wound is ready without fear of bacterial compromise.

Hyperbaric Oxygen

The roots of hyperbaric oxygen (HBO) can be traced to 1662 when Henshaw used compressed air to treat multiple diseases. In 1834 Junod treated pulmonary disease with two to four atmospheres of pressure in a hyperbaric chamber. From Junod's success the 1800's saw an explosion of hyperbaric chambers worldwide. Then in 1928 Cunningham constructed the largest hyperbaric chamber ever built. It was a giant sphere five stories high, **19.5 meters** in diameter with multiple floors, bedrooms and all of the amenities of a fine hotel. He treated such diseases as syphilis, hypertension, diabetes mellitus and cancer. In 1942 the American Medical Association condemned Cunningham's therapy after his failure to provide scientific evidence of its efficacy. In 1956 Boerera performed cardiac surgery in a hyperbaric chamber and in 1960 Sharp and Smith treated the first human with carbon monoxide poisoning. When Boerera used HBO to treat gas gangrene in 1961 the era of HBO use in wound healing began.[2]

Atmospheric pressure at sea level is 1 ATA. At this level the saturated blood oxygen concentration is 0.3ml per deciliter and tissues extract 5-6 ml of oxygen per deciliter of blood

with normal perfusion. This is only made possible because of the oxygen carrying capacity of hemoglobin. At 100% O_2 at 1 ATA the oxygen dissolved in blood is 1.5ml per deciliter and at 3 ATA it is 6 ml per deciliter.[51] At 3 ATA the dissolved oxygen is equal to what is normally extracted principally from hemoglobin at 1 ATA. Normal subcutaneous tissue oxygen tension is 30-50mmHg.[2] As described previously, most chronic wounds fail to heal because of local hypoxia. This low oxygen tension, typically **a partial pressure of oxygen** (pO_2) of 5-20mmHg, leads to anaerobic cellular metabolism, increase in lactate and a decrease in pH all of which inhibit wound healing.[2] Therefore, theoretically these wounds should improve with greater local oxygen delivery. This concept forms the current basis for hyperbaric oxygen therapy.

Oxygen is necessary for hydroxylation of proline and lysine, the polymerization and cross-linking of procollagen strands, collagen transport, fibroblast and endothelial cell replication, effective leukocyte killing, angiogensis and many other processes.[52] The optimal pO_2 for these processes, in healing wounds, is 50-100mmHg but many wounds will only reach 10-30mmHg.[2] Because the optimal dose of oxygen for nonhealing wounds has not been determined, therapy can be started with simple nasal cannula O_2 at six liters/min. at one ATA. With more persistent wounds HBO can be initiated.

The decision to utilize HBO is made after a vascular evaluation and transcutaneous oxygen (TcO_2) measurements. If the wound TcO_2 is >40mmHg HBO may be useful. If the TcO_2 measurement is <40mmHg a dive at 2.4 ATA is undertaken. If during this dive the wound TcO_2 is >1000mmHg HBO may be useful. But, if <1000mmHg it most likely will not.[2] Alternatively, if the wound TcO_2 improves by 10mmHg with 100% O_2 by nasal cannula, it is likely that HBO will be useful. With a successful trial, a treatment course is initiated. This involves the patient

lying in the hyperbaric chamber for one to two hours while breathing 100% O_2 at 2.0-2.4 ATA. Therapy is conducted daily for 10-70 days. This schedule correlates with the cell cycle of fibroblasts, which is approximately 24 hours with one hour in mitosis.[2] Hyperbaric oxygen increases the quantity of dissolved oxygen in the blood. At the standard 2.4 ATA the **arterial partial pressure of oxygen (PO_2)** is 1500mmHg. This increases the driving pressure for diffusion of oxygen into the tissue, the diffusion distance by three to fourfold and ultimately the wound pO_2 to 800-1100mmHg.[2,51]

There are many studies that have demonstrated benefit from hyperbaric oxygen therapy.[53-59] However, only two of these have been controlled studies.[59,60] Nevertheless HBO has been quite promising for many types of wounds. In fact, one study has demonstrated that when used in conjunction with certain growth factors, HBO was found to exhibit a "synergistic effect."[61] Despite its beneficial effects there are infrequent adverse effects. These may include reversible myopia, rupture of the middle ear or cranial sinuses, generalized self-limited seizures, tracheobronchial symptoms and claustrophobia.[62]

Electrostimulation

The foundation for electrostimulation in wound healing began in 1860 when DuBois-Reymond described the electrical currents within a human skin wound.[62] In 1910 Herlitzka measured this current at approximately 1μA.[62] Cunliffe and Barnes, in 1945, discovered that wounds had a positive potential compared to the surrounding intact skin.[63] In 1980 Illingworth and Barker found that a peak current of 22 μA cm^{-2} could be measured in the fingertips of children who had undergone accidental amputation.[64] Barker presented a map of human "skin battery" voltages in 1982.[64] He measured transcutaneous voltages up to 40mV and also noted that the skin surface

was always negatively charged when compared with the deeper skin layers.[65] These findings have lead researches and clinicians to examine the use of various forms of electrostimulation in chronic wound healing. Currently, there are four primary types of stimulation used: direct current, low-frequency pulsed current, high-voltage pulsed current and pulsed electromagnetic fields.

The most accessible and therefore earliest stimulation modality studied was direct current. This consists of placing a negative or positive electrode within the wound and the other electrode on the skin surface distant to the wound. A current of 0.03-1mA is passed across the wound for a period of one to three hours. This process is repeated one or more times daily until the wound is healed. In 1969 Wolcott presented the use of direct current therapy on 75 ischemic ulcers in 67 patients. His study protocol included reversing the wound electrode when a healing plateau was reached. He demonstrated favorable results when compared to controls.[66] His protocol, including reversing the electrodes, became the foundation for several studies that demonstrated a benefit to direct current.[67,68] In 1974 Rowley et al suggested that the negative electrode suppressed healing and infection while the positive electrode enhanced both.[69] Unfortunately, the lack of controlled studies and the availability of newer, more efficient forms of electrostimulation has resulted in a decline in the use of direct current today.

Low frequency pulsed current or tetanizing current has been widely used in the field of physical therapy. Patients with muscular or pain problems have used transcutaneous electrical nerve stimulation (TENS) for over 25 years. TENS is delivered via two electrodes placed on the skin surrounding the wound. A current of up to 50mA with a frequency of 2-100Hz is delivered in pulses of 45-500μs. This results in stimulation and contraction of the surrounding muscle and

therefore increased blood flow. Many studies have reported success with this form of therapy for pressure ulcers, especially in patients with spinal cord injuries.[70-72]

High-voltage pulsed current utilizes output voltages from 100-500V (typically <200) with a short pulse duration and a low current (15-40mA). The protocol originally described by Wolcott is typically used with the negative electrode placed in the wound and the positive lead at the skin edge. When a plateau in healing rate is reached the polarity is changed. Study results have been mixed but there appears to be an improved rate of healing when compared to controls with this form of therapy.[73-76]

Although the history of pulsed electromagnetic field (PEMF) therapy can be traced to Ginsberg in 1934, it wasn't until the late 1980's when clinicians took an interest in this form of therapy.[77] PEMF delivers 27.12 MHz of energy at a pulse rate of 80-600pps and a per pulse power range of 293-975 peak watts.[78] Therapy is administered via an applicator with a **23cm-diameter** treatment head for 30 minutes, twice daily until the wound is healed.[6] Initial reports have shown improved rates and overall healing when compared to placebo.[79-81]

Many studies have been undertaken to understand the mechanisms of wound healing by electrostimulation. These studies have identified different effects for negative and positive current. They have been summarized by Gentzkow as the following:[82]

<u>Negative Current</u>

- Decreases edema around the electrode
- Lyses or liquefies necrotic tissue
- Stimulates growth of granulation tissue
- Increases blood flow
- Causes fibroblasts to proliferate and make collagen
- Induces epidermal cell migration
- Attracts neutrophils

- Stimulates neurite growth directionally

Positive Current

- Promotes epithelial growth and organization
- Acts as a vasoconstrictor and induces clumping
- Denatures protein
- Aids in preventing post-ischemic lipid peroxidation
- Decreases mast cells in healing wounds
- Attracts macrophages

Both

- Stimulate neovasculature
- Have bacteriostatic effect
- Stimulate receptor sites for certain growth factors

Summary

Systemic diseases such as diabetes mellitus, peripheral vascular disease, autoimmune disease, neuropathy, steroid dependence and venous stasis contribute to chronic wounds. The net result is a non-healing wound with hypoxia, infection, edema and metabolic abnormalities. Standard wound care practice dictates that these wounds must first attain adequate blood supply, then undergo appropriate surgical debridement prior to initiation of adjuvant therapy. Additional therapy typically involves antibiotics and dressings to keep the wound physiologically moist. When the wound fails to progress despite optimal conservative therapy, then it is appropriate to apply one of these adjuvant modalities.

Although a common practice, the use of whirlpool may, for most patients, be more detrimental than beneficial. Alternatively pulsed lavage is fast becoming an efficient and productive tool for chronic wounds. Ultrasound appears to have beneficial effects but there is a paucity of carefully controlled studies to determine its effectiveness. Subatmospheric pressure therapy has became one of the mainstays of adjuvant therapy. It has yet to demonstrate significant adverse effects and produces clean, well-granulated wounds in a short period of time. Hyperbaric oxygen has

been shown to be as equally beneficial in certain wounds. Unfortunately, access to chambers and cost often make it difficult to use. Finally, electrostimulation has the potential to be highly useful and beneficial. More controlled studies comparing electrostimulation to other forms of therapy need to be undertaken.

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