Wound Healing Devices Brief Vignettes

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Significance: The demand for wound care therapies is increasing. New wound care products and devices are marketed at a dizzying rate. Practitioners must make informed decisions about the use of medical devices for wound healing therapy. This paper provides updated evidence and recommendations based on a review of recent publications.

Recent Advances: The published literature on the use of medical devices for wound healing continues to support the use of hyperbaric oxygen therapy, negative pressure wound therapy, and most recently electrical stimulation.

Critical Issue: To inform wound healing practitioners of the evidence for or against the use of medical devices for wound healing. This information will aid the practitioner in deciding which technology should be accepted or rejected for clinical use.

Future Directions: To produce high quality, randomized controlled trials or acquire outcome-based registry databases to further test and improve the knowledge base as it relates to the use of medical devices in wound care.

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SCOPE AND SIGNIFICANCE

THIS MONOGRAPH AIMS to provide the wound care practitioner with a succinct and updated evaluation of popular nonpharmacologic wound therapies.

The practitioner must be up to date on the level of evidence and class of recommendation related to these devices so as to maximize patient benefit and resource utilization.

TRANSLATIONAL RELEVANCE

Techniques reviewed here have ample basic science evidence to support potential application to the clinic. While this is supportive only through the completion of well-designed controlled clinical trials should a new therapy become widely accepted into practice.

CLINICAL RELEVANCE

Practitioners are routinely exposed to an array of wound healing devices. It is difficult to weigh the potential benefits and risks related to a particular technique and wound

BACKGROUND

Methodology

The grading of evidence and recommendations used for this monograph follows that adopted by the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines in 2013.¹ Briefly, the level of evidence is rated A, B, or C based on the precision of the supporting study design (A= multiple populations studied with randomized controlled trials [RCTs] or meta-analyses, B= limited populations with single RCT or nonrandomized studies, C= limited populations, case reports, or consensus opinion). The class of recommendation is based on the size of

the treatment effect, weighing relative benefits versus risks (I = the treatment should be used, IIa = it is reasonable to use the treatment, IIb = the treatment may be considered, III = not recommended as there is a risk of harm and no potential benefit). The recent literature was searched using the PubMed search engine from calendar years 2005 to 2015.

DISCUSSION

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBOT) is defined as exposure to 100% oxygen at greater than 1 atmosphere of pressure (>760 mmHg). HBOT plays an adjunctive role in the management of acute and chronic wounds. The potential risks of HBOT are relatively small and contraindications are rare.² Exposure to increased barometric pressure inside a hyperbaric chamber increases the oxygen content dissolved in plasma. The dissolved oxygen is the metabolically active fraction of oxygen that can now penetrate tissues compromised by chronic or acute inflammation, tissue edema, and microvascular thrombosis or rarefaction. There are multiple mechanisms of action of HBOT, including reduction of leukocyte adhesion to vascular endothelium and increase in tissue levels of nitric oxide, hypoxia inducible factor-1, and vascular endothelial growth factor.³ The induction of neoangiogenesis and vasculogenesis is observed and is related to the stimulation of bone marrow-derived progenitor cells.⁴ HBOT has antimicrobial effects and increases intracellular leukocyte killing by the oxygen-dependent peroxidase system.⁵ To benefit wound healing, daily treatments range from 20 to 60 sessions. Typical doses and durations range from 2.0 to 3.0 atmospheres absolute for a total of 60–120 min. Rigorous comparison of dose responses and treatment algorithms is lacking.

Undersea and hyperbaric medicine society-approved indications⁶

Enhancement of healing in selected problem wounds: diabetic foot ulcer. Wounds that fail to progress through the normal phases of healing demonstrate significant tissue hypoxia due to poor local perfusion.^{7,8} The diabetic foot ulcer (DFU) has become a major focus of HBOT and research. Several RCTs report favorable effects on DFU healing.^{9,10} Centers for Medicaid and Medicare Services (CMS) cover HBOT for DFUs that have failed 30 days of standard wound care and show evidence of deep soft-tissue infection, osteomyelitis, or gangrene (Wagner Grades 3,4,5) (Level/Class: A/I).

Delayed radiation tissue injuries/late effects of radiation therapy. Delayed radionecrosis of skin is an adverse event of radiation therapy, which re-

sults in painful fibrotic wounds that do not heal with standard care. Late effects of radiation therapy cause obliterative endarteritis leading to tissue hypoxia and fibrosis. The foundational studies by Dr. R. Marx have been substantiated by more recent data.^{11–14} This beneficial effect was dependent on good surgical and medical care in conjunction with HBOT. HBOT does not replace the basic need for timely surgical debridement and antimicrobial therapy (Level/Class: B/IIa).

Crush injuries and skeletal muscle-compartment syndrome. Surgical and traumatic wounds generally heal with standard wound care. In compromised hosts, severe infection or situations of increased tissue tension, normal healing mechanisms fail due to tissue hypoxia. An acute ischemia–reperfusion cascade generates an overwhelming inflammatory response leading to capillary leak, tissue edema, and microvascular thrombosis. Timely HBOT counteracts this cascade by penetration of dissolved oxygen into the damaged tissues. Evidence consists of many uncontrolled clinical reports, two small RCTs, and one evidence-based review showing benefits.^{15–17} HBOT does not replace the need for surgical decompression for acute compartment syndromes (Level/Class: B/IIa).

Necrotizing soft-tissue infections. There is a wide array of necrotizing soft-tissue infections. These life- and limb-threatening conditions require major surgical debridement and have severe impairments in wound healing. The pathophysiology includes local tissue hypoxia secondary to severe edema, inflammation, and microvascular thrombosis. The cornerstones of therapy include wide surgical debridement and antibiotic therapy. Adjunctive timely HBOT helps control infection and reduce tissue loss. There are hundreds of positive case reports, multiple non-randomized clinical trials, and one meta-analysis suggesting that HBOT is associated with a significant reduction in mortality and morbidity.^{18,19} A recent analysis of the University Health Consortium database demonstrated a significant survival benefit for the subset of patients with the most extreme illness severity. A mortality rate of 4% was reported for the HBOT-treated group versus 23% for those not receiving HBOT, $p < 0.01$ ²⁰ (Level/Class: B/IIb).

Thermal burns. Thermal burn wounds are characterized by a marked inflammatory response and microvascular damage that lead to severe tissue edema, hypoxia, and vulnerability to invasive infection. An impaired leukocyte function further increases the risk for burn wound infection and sepsis. Human studies ranging from case series to

RCTs have supported the benefit of HBOT in burn wound management. Cianci *et al.* have reported a significant reduction in the length of hospital stay and need for surgery²¹ (Level/Class: B/Iib).

Compromised flaps and grafts. Surgical flap and graft compromise is initiated by acute ischemia-reperfusion injury and leads to a robust acute inflammatory response, tissue edema, increased mechanical tension, and impairment in microcirculation. These factors lead to worsening of tissue hypoxia and acidosis and threaten flap survival. HBOT plays a limited role, if any, in the support of split-thickness skin grafts (STSGs). There are currently no RCTs testing the effect of HBOT on full-thickness skin grafts or for myocutaneous flap survival in humans. The use of HBOT is supported by small case series and animal work²² (Level/Class: C/Iib).

NEGATIVE PRESSURE WOUND THERAPY

Negative pressure wound therapy (NPWT) provides multiple unique mechanisms to aid wound healing. Primary mechanisms of action are due to physical effects on tissues (Fig. 1). Macrodeformation causes a reduction in wound volume, and microdeformation induces changes in cytoskeletal structure, enhances cell-to-cell interactions, and stimulates cell division.²³ Another effect is the removal of excess tissue edema and inflammatory exudate. Perfusion about the wound bed margins may be enhanced or reduced and is a subject of debate.²⁴

NPWT-chronic wounds

Several RCTs have been reported. Fifty-four patients were randomized to NPWT versus gauze

therapy. The rate of wound area reduction was significantly greater in the NPWT group (3.8% per day vs. 1.7% per day, $p < 0.05$).²⁵ Another study allocated 65 patients to NPWT versus modern dressings.²⁶ No significant difference in time to complete granulation. A third study included leg ulcers in hospitalized patients. Mean time to complete healing with NPWT was 29 versus 45 days for controls ($p = 0.0001$)²⁷ (Level/Class: A/Iib).

NPWT-diabetic foot ulcer

There are more than 10 prospective clinical trials which include DFUs, only a few are randomized and controlled. Two relatively large RCTs evaluated NPWT in DFUs and showed benefits. The first study addressed partial foot amputations.²⁸ Wound healing was greater in the NPWT group at 56% versus 39% for controls, $p = 0.04$. Time to achieve the wound bed preparation decreased from 84 days for controls to 42 days for NPWT, $p = 0.02$. The second trial showed a statistically significant increase in the number of wounds healed with NPWT (42%) compared to moist dressings (28%).²⁹ A significant decrease in time to complete wound closure was reported in the NPWT group (median 96 days) versus median not reached by 16 weeks for controls (Level/Class: A/I).

NPWT-pressure ulcer

There are three reports on Stage III and IV pressure ulcers (PUs). A nonrandomized controlled trial comparing NPWT to conventional dressings showed a significant reduction in wound size with NPWT.³⁰ Another RCT that compared NPWT to modern dressings reported a reduction in the mean ulcer volume from 42% in controls to 52% for NPWT, not statistically significant ($p = 0.46$).³¹ Finally, a pro-

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Figure 1. Mechanical mechanisms of negative pressure wound therapy. Provided by KCI Corp. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

spective observational study reported by the Department of Veterans Affairs found no significant effect on healing of Stage III/IV PU.³² Given the small size of these trials and conflicting results, no recommendations can be made (Level/Class: B/None).

NPWT-split-thickness skin graft

NPWT provides stable fixation of STSG. The NPWT dressing immobilizes the graft, reducing shear motion and fluid accumulation beneath the graft. Two well-designed and implemented RCTs (total $n = 124$ grafts) reported a statistically significant improvement in graft take and decreased time to healing^{33,34} (Level/Class: A/IIa).

ULTRASOUND THERAPY

The Food and Drug Association (FDA) classifies US devices as Class II medical devices and has cleared several devices for wound therapy. A review of the individual devices is beyond the scope of this presentation.[†] Typical therapeutic US frequencies fall in the range of high-frequency ultrasound (HFU, 0.7–3.3 MHz) or low-frequency ultrasound (LFU 20–40 kHz). The depth of penetration ranges from 2 to 5 cm. Therapeutic US has both thermal and nonthermal effects. The absorption of HFU can produce thermal effects. Nonthermal effects are produced by LFU and are related to principals of cavitation, standing waves, acoustic streaming, and microstreaming.³⁵ US provides direct physical stimulation of cells and stimulates repair and healing processes.³⁶ The nonthermal effects of US are used for wound debridement and may have additive bactericidal properties.³⁷ The selection of exposure time and intensity level can significantly alter therapeutic effects. Most devices provide LFU (nonthermal, 20–40 kHz) and are used for wound debridement.³⁸ No standard prototypical algorithm has been reported in the literature.

US-DFU and venous leg ulcer

Ennis *et al.* reported a multicenter double-blinded RCT of US therapy for the treatment of chronic DFU. US did not achieve a statistically significant improvement in wound closure rates.³⁹ Watson and Kang'ombe assessed the clinical effectiveness of weekly delivery of low-dose HFU for treatment of venous leg ulcer (VLU) in a multicenter RCT. No difference in time to complete healing or evidence of a difference in rates of recurrence of healed ulcers (17/31 with US vs. 14/31 with standard care) was observed. Moreover, they reported significantly more

adverse events in the US group.⁴⁰ The Wound Healing Society Guidelines (2006) did not evaluate the use of US for DFUs or PUs. However, the WHS did assign Level I to its *lack* of statistically significant effect on healing VLUs (Guideline #7b.5) and Level III C for arterial insufficiency ulcers (Guideline #6. A.1).⁴¹ CMS reviewed US therapy and failed to cover this service. The National Institute for Health and Clinical Excellence guidance concluded that the relative effectiveness remains insufficient at this time to support routine use⁴² (Level/Class: C/III).

ELECTRICAL STIMULATION[‡]

A natural electrical gradient exists between the outer surface of intact skin (positive charge) and the subepidermal tissues (negative charge) and measures ~ 40 – 100 mV.⁴³ Any breach in the epidermal barrier leads to a loss of polarity and a mild electrical current then flows outward from the wound creating what has been termed “a current of injury.”⁴⁴ The electrical current generated by wounding has been shown to stimulate multiple cell types within the wound environment. Electrical stimulation (eStim) is one type of electrical therapy. Many additional forms of electrical therapies exist such as functional electric stimulation, neuromuscular electric stimulation, peripheral nerve stimulation, and electromagnetic therapy, and are not addressed here. The FDA clearance classifies eStim devices as Class II medical devices. eStim applies an electrical current across the wound bed using one positively charged electrode (cathode, aka active electrode) and one negatively charged electrode (anode, aka grounding electrode). The dose range of electricity commonly used is a low-intensity (continuous or pulsed) microcurrent and can be up to 1 mA.⁴⁵ The delivery of energy can be varied based on wave forms, frequencies, pulse duration, and polarity. eStim is a single clinical term; however, there exists a multitude of varied currents and dosages.[§] A prototypical algorithm reported in the literature for the acceleration of chronic wound healing is low-intensity current (direct or pulsed, 0.2–0.8 mA) delivered for 2 h twice or thrice per day, 5 days/week for 5–9 weeks.

Evidence

Numerous publications exist describing the use of eStim in multiple clinical settings, including ortho-

[†]Representative examples include: MIST Therapy System by Celleration, Inc., Sonica 185 by Soring, Inc., and Quostic Wound Therapy System by Arobella Medical, LLC.

[‡]Only electrical stimulation as a type of electric therapy will be addressed by this overview and is distinct from electromagnetic field therapy.

[§]Direct current, pulsed current, alternating current, low-intensity direct current, low-intensity pulsed direct current, high- or low-voltage pulsed current, frequency rhythmic electrical modulation systems, biphasic and monophasic pulsed current, and others.

pedics, physical therapy and rehabilitation medicine, pain management, and wound healing. These papers address the effects of eStim on cells and tissues in both animals and humans.^{46,47} Several systematic reviews of human clinical trials arrived at similar conclusions: There is a clinical benefit for eStim treatment of wounds in humans.^{48–50} Wound diagnoses tested include DFU, VLU, and PU. Each has small, randomized controlled clinical trials that show some degree of benefit. The Wound Healing Society Guidelines assigns Level I evidence for the use of eStim therapy in VLU (#7b.4), PU (#7b.2) and DFU (#7.7)⁴¹ CMS accepts eStim as a covered service (Level/Class: Level A/Class IIa).

THERMAL THERAPY

Warming wounds by direct noncontact radiant heat or by indirect global warming has been employed for years in an effort to restore normothermia to the wound bed. Due to the lack of evidence of benefit in multiple RCTs, CMS discontinued coverage and the manufacturer withdrew the only wound warming device (WarmUp[®]) from the US market in 2002. There is insufficient evidence to grade or recommend thermal therapy at this time (Level/Class: None/not done).

SUMMARY

Despite the existence of evidence-based reviews, guidelines, and recommendations, the interested wound care practitioner must be informed about the particular device and the patient population for which it is intended. The rigorous nature of RCTs provide scientific efficacy, however, the practitioner must understand the concept of generalizability as it applies to their patient population if effectiveness is to be attained. Finally, the general lack of reporting of adverse events associated with the devices included in this review mandates that adopters of these technologies put systems in place to adequately monitor adverse outcomes over time.

TAKE-HOME MESSAGES

Based on the current 2015 evidence, should I consider providing the following therapies to my patients?

YES for: HBOT, NPWT, and eStim

NO for: US and thermal therapy

Disclaimer: The authors recognize and credit the existence of the multiple recent and extensive reviews covering each of the technologies included here. The aim of this monograph is to streamline this information to guide the busy clinician. Readers seeking more in depth information are directed to the usual resources, such as PubMed literature search, society-based guidelines, and systematic reviews of the literature.

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Abbreviations and Acronyms

CMS = Centers for Medicaid and Medicare Services
 DFU = diabetic foot ulcer
 eSTIM = electrical stimulation
 FDA = Food and Drug Association
 HBOT = hyperbaric oxygen therapy
 HFU = high-frequency ultrasound
 LFU = low-frequency ultrasound
 NPWT = negative pressure wound therapy
 PU = pressure ulcer
 RCT = randomized controlled trial
 STSG = split-thickness skin graft
 VLU = venous leg ulcer