

Methodologies of Biophysical Wound Healing Therapies

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Abstract

Purpose: To evaluate the effects of methodological variation of biophysical therapies on wound healing outcomes, as a preliminary study to develop a composite wound healing device. **Methods:** A literature search was focused on the variable devices, system configurations, input parameters, and treatment durations of negative pressure wound therapy (NPWT), electrical stimulation (ES), and low-level light therapy (LLLT) from 2011 to July 2016. **Results:** In NPWT, lower vacuum pressures of -50 and -80 mmHg achieved similar tissue perfusion outcomes as earlier recommendations of -125 mmHg, while there is no established regimen with respect to continuous, square wave, or triangular NP waveform due to inconsistent results. Use of wound filler may contribute to improved tissue granulation when compared to topical NP. An ES configuration of high-voltage pulsed current with the stimulation electrode placed in the wound bed best resembles the endogenous skin current, which guides cellular migration. However, no studies have established optimal stimulation parameters. For LLLT, laser and LED proved similarly effective. Although red light has been almost exclusively used in human pressure ulcer treatment, studies comparing blue, green, and red wavelengths more consistently show biological effects using green light. **Conclusions:** Variation in the application of mechanical, electrical, and radiant energies may be used to modulate wound healing pathways. To 2012, no studies have examined use of these biophysical modalities in combination. Further methodological studies with a systems approach would help define optimal treatment protocols for improved wound healing outcomes in clinical practice.

Keywords

Wound Healing, Therapy, NPWT, HVPC, LLLT, Methodology, Review

1. Introduction

During 2012, approximately 200,000 new patients were added to the growing number of 780,000 Germans living with unhealed wounds for three months or more [1]. Half of these patients received treatment, however as chronic wounds represent a disruption in normal healing pathways, additional treatment beyond standard care wound dressings may be required to complete healing. In response to this clinical need, advanced care technologies are being developed to heal refractory venous leg, diabetic foot, and pressure ulcers.

These treatments may involve application of mechanical, light, or electrical energy to the wounded skin. For example, negative pressure wound therapy (NPWT) applies vacuum pressure to a filled and sealed wound bed, while also removing tissue exudates. Electrical stimulation (ES) applies imperceptible electrical fields across the wound tissue, while low-level light therapy (LLLT) applies blue to near infrared light. Such biophysical-tissue interactions have been shown to re-stimulate the natural healing pathways.

Detailed knowledge of the pathways stimulated by these treatment modalities is growing. NPWT provides fluid removal, yet also derives efficacy from macro- and micro-deformation, the latter being transferred to single cells by the ECM and potentially the integrin-mediated interaction of the cell with the matrix [2]. ES seems to act by enhanced recruitment of mast cells to the wound that may be mediated by so far poorly understood pathways of electrotaxis [3]. Finally, LLLT seems to be acting at least in part through mitochondrial pathways and the generation of reactive oxygen species, the generation of ATP, and the stimulation of transcription factors [4].

Although increasing evidence supports the clinical usage of these therapies, routine treatment protocols have not yet been established. Importantly, variations of equipment and technique may introduce variations at the wound surface that influence healing. Therefore, this review evaluates the effect of variations in methodological approaches of NPWT, ES, and LLLT on healing pathways. Such developments would help define the wound system, establish primary biophysical-tissue interactions, and develop optimized protocols for specific wound healing needs leading towards broader adoption into clinical practice for improved care of chronic wounds.

2. Literature Search

This work is a preliminary study towards the design of a composite biophysical wound healing device. Thus, a PubMed database search from 2011 to July 2016 was conducted for reviews in English of NPWT (243 results), ES and wound (200 results), and LLLT and wound (51 results). Notably, selection criterion was for reviews focusing on studies of the effect of variable methodologies on outcomes, rather than efficacy. Therefore, 1 paper was selected for NPWT [5], 0 for ES, and 1 for LLLT [6]. Finally, the search criteria were relaxed to include reviews of the efficacy of ES, while also including a recommendation for selecting stimulation parameters; thus, 2 relevant LLLT review papers were selected. In total, these reviews provided 130 studies of variable methodology

which were previously reviewed through July 2016. Therefore, this work provides a summary through 2010 (NPWT), 2013 (ES), and 2012 (LLLT) of the effect of methodological variation on wound healing outcomes.

All 43 NPWT studies were in *in vitro* cell systems or in *in vivo* animal models; no clinical data were available. Most studies were in porcine models, while tissue perfusion was a commonly reported outcome. Laser and LED were compared in *in vitro* and *in vivo* mouse and rat animal models. Additional methodological studies in the LLLT review were selected, which used a range of either wavelength or dosage, and reviewed independently. For ES, 1 paper reviewed randomized controlled trials (RCTs) and observational studies for pressure wounds [7] and the other reviewed 10 RCTs on pressure ulcer, chronic leg ulcers, and diabetic foot ulcers [8].

3. Results

3.1. Mechanical

Study results are summarized in **Table 1**. Amongst the 14 available NPWT systems, no studies have statistically compared device performances or wound interface materials. Transmission of NP is more efficient through perforated drainage conduits inserted into various wound fillers than through a non-perforated drain [9].

As compared to the Redon drain (topical NP), NPWT transmitted through wound fillers results in significantly greater tissue granulation in human sacral pressure ulcers [10]. Both gauze and foam transmitted NP efficiently [11]-[13]; there is no evidence to favor a particular wound filler [5]. However, some preclinical evidence suggests the use of foam may preferentially promote cell proliferation as compared to gauze [14]-[17].

Across a range of NP magnitudes, maximum peak tissue perfusion was initially achieved at -125 mmHg [23]. Yet, subsequent studies of NP magnitude have achieved similar tissue perfusion, granulation tissue formation, and wound closure outcomes to -125 mmHg at -80 mmHg [11] [15] [21] [22] and at -50 [12] [18]-[20]. Studies of NP continuous, square wave, and triangular waveforms have resulted in inconsistent granulation tissue formation outcomes [23] [24]. Thus, new evidence supports the use of a

Table 1. The variable equipment and techniques studied in negative pressure wound therapy (NPWT).

Mechanical	<i>In vitro</i> and <i>in vivo</i> porcine model results [2]		
	Options	Notes	Selection
Devices	14 NPWT systems or Redon drain	Wound filler or topical NP only	NPWT [10]
Wound filler	Foam or gauze	Foam and tissue Granulation [14]-[17]	Either [5]
Interface material	Impregnated gauze	No statistical studies	Inconclusive
Drainage conduit	Perforated or non-perforated	Within or on top of wound filler	Perforated [9]
NP magnitude	-25 mmHg to -400 mmHg	Tissue perfusion modulation	-50 [12] [18]-[20] to -80 mmHg [11] [15] [21] [22]
NP waveforms	Continuous, square, or triangular wave	Inconsistent results [23] [24]	Inconclusive
Treatment duration	Study duration only	-	Inconclusive

lower NP magnitude, while there is insufficient evidence to define a NP waveform regimen.

3.2. Electrical

Electrode placement in the wound most resembles the skin endogenous electrical field to improve healing rates [25]-[27]. AC stimulation [28] and asymmetric AC pulses [29], resulted in faster healing rates than DC waveforms. Variations in applied voltages [30] and stimulation duration [31] demonstrated a dose-dependent induced cell migration of keratinocytes and fibroblasts [32], respectively. Thus, high-voltage pulsed current (HVPC) stimulation has emerged as a treatment modality with the most clinical potential for use in chronic wound healing, while also minimizing the risk of burns and having a greater depth of current penetration [33] [34].

No studies have compared the methodological parameters of HVPC on wound healing outcomes. Thus, only HVPC parameter ranges can be reported. The commonly used HVPC parameters are summarized in **Table 2**.

3.3. Radiant

Study results are summarized in **Table 3**. Laser or LED devices differ by their emission mechanisms, however any differences in their light properties are lost during photo-tissue interactions [35] [36]. Accordingly, studies comparing laser and LED for LLLT application have resulted in similar biological effects [6].

All studies comparing the biological effects of blue, green, and red wavelengths for LLLT application showed the effectiveness of green light, while results are inconsistent for blue and red light. In particular, green and red light but not blue light were effective, on increasing fibroblast numbers [37], migratory or proliferative effects [38], or increased angiogenesis [39]. In contrast, green and blue light were effective, but not red

Table 2. The variable equipment and techniques studied in electrical stimulation (ES).

Electrical	Human pressure ulcer results [4] [5]		
	Options	Notes	Selection
Electrode configuration	Treatment electrode in wound or all electrodes surrounding wound	Resembles skin electrical current	Electrode in wound [25]-[27]
Waveform	DC, DC pulse, Symmetric AC pulse, Asymmetric AC pulse, High-voltage pulsed current (HVPC)	Faster healing rates	HVPC [28]-[33]
Stimulation electrode	Anode or cathode	Alternative healing pathways	Inconclusive
Stimulation parameters	50 - 100 μ s double-peaked impulses 80 - 105 pulse per second frequency 50 - 200 V voltage 2 - 2.5 A peak-current amplitude	No optimization studies	Inconclusive
Treatment duration	45, 60, 120 minutes	Wound closure	60+ minutes [31]

Table 3. The variable equipment and techniques studied in low-level light therapy (LLLT).

Radiant	<i>In vitro</i> and <i>in vivo</i> mouse and rat model results [3]		
	Options	Notes	Selection
Device	Laser or light-emitting diode (LED)	Similar effects at similar settings	Either [6] [35] [36]
Wavelength	Blue, green, red, near infrared (456 - 1064 nm)	Wavelength-dependent tissue chromophores	Green [37]-[41]
Dose	0.09 - 90 J/cm ²	Dose-dependent activation and inhibitory effects	Up to 5 J/cm ² [6] [42]-[46]
Treatment duration	1 - 2, 5 - 10, 60 - 120 minutes	Varying irradiance, constant energy density	10 minutes or less [47]

light, in decreasing wound size [40] or increasing healing rate [41]. Dose values up to 5 J/cm² produced the most significant biological effects [6]. In particular, doses of 4 J/cm² are more effective than 8 J/cm² [42], while doses of 10 and 16 J/cm² promoted inhibitory effects [43]-[46]. Finally, variance in output power and exposure time can be modulated to achieve a specified energy density and as a result influence outcomes [47].

4. Discussion

The influence of varying negative pressure and strain on tissue perfusion outcomes has been well explored in animal models. Data collected to date suggest the use of wound filler may promote tissue growth. Application of lower NP magnitudes achieved results similar to those at higher NPs; however, a NP waveform regimen has not been optimized. Interestingly, the use of wound filler in NPWT may be associated with promotion of tissue growth. Therefore, more understanding of the physical effect of foam and negative pressure on the internal tissue and vessel pressures, as well as at the cellular level would help in tailoring wound healing needs, in particular, through the modulation of tissue growth and perfusion.

With an appropriately selected electrode configuration and waveform type, application of electrical energy resembles the endogenous skin current. Thus, HPVC has emerged as the leading ES type for healing in human pressure ulcers. However, the lack of methodological studies on the input parameters of HVPC indicates an opportunity for further development. Ongoing debates in this field involve the selection of the anode or cathode electrode for activation, where effects broadly diverge between immune or remodeling healing pathways [48].

In LLLT the use of both laser and LED promote healing and the primary photo-tissue reactions of wavelength-specific light absorption by skin chromophores are well studied. Yet, the exact biological mechanisms resulting in enhanced proliferation are still only partly understood. Interestingly, although red light has almost exclusively been used in human applications, studies using blue, green, and red wavelengths have more consistently resulted in biological effects with green light.

More recent methodological studies, which have not yet been reviewed in the literature, will be more extensively searched and reviewed in the future. While there is an abundance of literature analyzing the effect of each of the above treatment modalities, through 2012, a combination of biophysical modalities for wound healing was not stu-

died. Specification of such a device should include consideration of the results of these comparative modes, devices, and parameters. Perhaps due to the particular advantages of each biophysical modality—tissue perfusion and edema reduction, immune and cellular stimulation, and reactivation of healing processes—a wisely selected combination of modalities may hold great potential for a significant improvement in the treatment of chronic wounds. Finally, unified reporting of methodological inputs, specifically as biophysical energies, dosages, and treatment durations would greatly contribute to the development of a wound model for control and modulation of wound healing outcomes, as well as a system for studying fundamental biophysical-tissue interactions.

5. Conclusions

Mechanical, electrical, and radiant biophysical energies have been used to successfully re-activate wound healing pathways. Variations in their input parameters produce variations in cellular responses, which can be modulated and possibly combined to achieve wound-specific healing outcomes. Further methodological studies with a systems approach would help define treatment protocols and facilitate the adoption of biophysical wound healing treatments into clinical practice for improved wound healing outcomes.

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