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Physical Modalities in the Management of Wound(s)

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Abstract

Wound is caused by disruption of the integrity of body skin as a result of environmental or medical factors. Managing chronic and refractory wounds is a significant dilemma physicians are facing. Large varieties of treatment modalities have been used to enhance wound healing among which were different medicines, surgical procedures, physical therapy, hyperbaric oxygen therapy, and physical modalities such as laser and shockwave. In this chapter, the authors discuss physical modalities that are most used in the management of wound healing with a focus on lasers, shockwaves, photodynamic therapy, UVB therapy, and lights and describe some important experimental and clinical trials that have been done in this regard with an attempt to explain their mechanisms.

Keywords: wound healing, low-level lasers, shockwave, photodynamic therapy, phototherapy, CO₂ laser

1. Introduction

Wound is caused by disruption of the integrity of body skin as a result of environmental or medical factors. Managing chronic and refractory wounds represents a significant dilemma that physicians are facing. Wound healing is a complex cascade of events that restores skin integrity by replacing damaged cells and tissues which consists of four phases: hemostasis, inflammation, proliferation, and remodeling. In the first phase, hemostatic changes result in a reduced blood flow and clot formation. Activated platelets as well as the injury itself attract inflammatory agents, neutrophils, and predominantly macrophages, which clear the apoptotic cells. By releasing growth factors, these leukocytes trigger proliferation of fibroblasts, epithelial and

endothelial cells in the trauma site forming the granulation tissue. Turnover of collagen from type III to I restores skin integrity in the remodeling phase. Various factors can influence the quality of wound healing including nutrition, vitamin deficiencies, smoking, sex hormones, oxygenation, age, stress, diabetes, alcoholism, and medications such as glucocorticoid steroids, chemotherapeutic agents, and nonsteroidal antiinflammatory drugs [1].

Large varieties of treatment modalities have been used to enhance wound healing such as different medicines, surgical procedures, physical therapy, hyperbaric oxygen therapy, and physical modalities such as laser and shockwave. Some substances like honey have also proved to be beneficial in wound healing as a result of antiinflammatory and antibacterial features [2]. The ideal physical therapy modality is chosen based on the patient's factors, type of wound, previous therapies, and clinician's preference.

Electrical stimulation is another method of physical therapy used for accelerating wound healing. Electrotherapy works by stimulating cell migration, cell proliferation rate, and growth factor secretion via creating an electrical current. The anode attracts macrophages, neutrophils, and keratinocytes. The cathode attracts activated neutrophils, fibroblasts, myofibroblasts, and endothelial cells [3].

Low-level laser therapy (LLLT) is also a novel approach for treating wounds. Greatest benefits have been achieved through wavelengths of 632–1000 nm. The mechanism of action of LLLT is defined through wound contraction which accelerates the wound healing process [4].

Pulsed radiofrequency energy also promotes chronic wound healing by contracting the wound [5]. It has minimum side effects as well as the advantage of reducing wound pain.

Light-emitting diode (LED) has somewhat similar effects as light amplification by stimulated emission of radiation (LASER) in expediting the process of wound healing by increasing fibroblasts and collagens and decreasing inflammatory cells in the trauma site [6].

Shockwaves have also proved to be beneficial in overcoming chronic and intractable wounds such as diabetic ones with minimal adverse effects and long-lasting results. The mechanism through which they work remains unknown; however, several factors are considered to be effective in this procedure including stimulation of microcirculation and metabolism, reduction of inflammatory cells, release of growth factors, and stimulation of stem cells [7].

Photodynamic therapy (PDT) has also proved to be effective in wound healing. However, it seems to display best results when used in conjunction with lasers [8].

The effect of ultraviolet therapy on wound healing seems not promising and may even delay the process as it has shown to affect focal adhesion dynamics [9]. On the other hand, there are studies which suggest that ultraviolet C can be beneficial in expediting wound healing with antibacterial effects [10].

In this chapter, the authors tend to discuss physical modalities that are most used in the management of wound healing with a focus on lasers, shockwaves, photodynamic therapy, UVB therapy, and lights.

2. Low-level laser and wound healing

In the recent years, it has been shown that the laser therapy had the potential to improve wound healing and reduce pain and inflammation [11].

The main indications of low-reactive-level laser therapy (LLLT) are reduction of pain and inflammation. It amplifies tissue repair, enhances regeneration of different nerves and tissues, and prevents tissue injury in situations where it is likely to occur [12, 13].

Low-reactive-level laser therapy (LLLT) enhances the activation of intracellular or extracellular chromophores and the initiation of cellular signaling by exposing cells or tissue to low levels of red and near infrared (NIR) light [11]. The biological effects of LLLT are decreased inflammatory cells, increased fibroblast reproduction and angiogenesis, and stimulation of granulation tissue and augmented collagen synthesis [14].

LLLT assumes the use of photons at a nonthermal irradiation to alter biological activity. LLLT is composed of two sources: coherent light and noncoherent light sources (lasers) consisting of filtered lamps or light-emitting diodes (LED) or, on occasion, a combination of both [13, 14].

The reason of the term “low level” is the use of low-power contents compared to the other forms of laser therapy such as cutting, ablation, and thermally coagulating tissue.

The mechanism of LLLT on wound healing is not yet fully understood nevertheless it appears that LLLT has a wide area of effects at all the levels of molecular, cellular, and tissue ingredients. The main biological mechanism behind the effects of LLLT is proposed to be absorption of red and NIR light by mitochondrial components, in particular cytochrome c oxidase (CCO) which is concluded in the respiratory chain located within the mitochondria [15–17], and also in the plasma membrane of cells. Accordingly, a chain of events and various process carries out in the mitochondria [18] leading to wound healing.

Although LLLT is now used as a portable minimally invasive, easy-to-use, and cost-effective modality to promote wound healing, it is also employed for treatment of diabetic lower extremity ulcer. However, it remains controversial in this therapy for two reasons. First, there are uncertainties about the basic molecular and cellular mechanisms responsible for appropriate biological effects on the affected tissue. Second, there are significant variations in terms of parameters measuring: wavelength, irradiation or power density, pulse structure, coherence, polarization, energy, fluence, irradiation time, contact versus noncontact application, and repetition regimen. Lower level parameters can result in lower impact of the treatment and higher ones can lead to tissue injury [12, 14].

Inappropriate choice of light source and dosage can be the cause of negative results of many of the published studies on LLLT. In addition, eventual mismatch of the patient's skin to the application of LLLT were described, such as: improper preparation and oily debris that can interfere with the influence of the light source, and cause failure to account for skin pigmentation [19]. Unsuitable maintenance of the LLLT devices can reduce its efficiency and interfere with clinical results as well. It is important to notice that there is an optimal dose of light for any particular issues [14].

Nevertheless, many systematic reviews point that LLLT is an effective therapeutic modality on wound healing and diabetic foot ulcer recovery [20], but additional clinical studies must be performed in order to find out the best parameters of wavelength, dosage, and methodology and especially appropriate treatment protocol.

3. Relative contraindications/precautions

3.1. Relative contraindications

3.1.1. Cancer

Do not use LLLT over any known malignant lesions unless: for pain relief during the terminal stages of the illness, and for cancer therapy side effects (e.g., oral mucositis, radiation dermatitis, etc.).

3.1.2. Pregnancy

There is no evidence of harm to an unborn baby; however, there are no safety tests either, so for medico legal reasons it is recommended to not treat directly over the developing fetus.

3.1.3. Thyroid

Although relatively low intensity is far less likely to trigger any adverse events when treating that region of the neck, we suggest not applying lasers directly over the thyroid.

4. Photodynamic therapy and wound healing

Photodynamic therapy (PDT) as a photochemistry process can kill cancer cells, inactivate infected pathogens, and demolish target tissue. In PDT process, one special material called photosensitizer or nontoxic dyes absorbs visible light and produces excited singlet state such as singlet oxygen and hydroxyl radicals that are able to attack to target cells [21]. Administration of photosensitizer either topically or systemically in combination with irradiation appropriate wavelength laser is a promising treatment modality in wound healing especially for chronic pressure and decubitus wounds frequently encountered in diabetic and disable patients. The healing of chronic wounds and venous stasis ulcers of the leg is compromised by infection, yet PDT has an antimicrobial action [22]. Bacterial burden in chronic ulcer decreases by treatment with infrared radiation. A radiation via endogenous protoporphyrin (and/or protoporphyrin IX [PpIX] of bacteria) is virtually similar to a mild PDT [23]. It appears that PDT with suitable PS together with suitable laser parameters represents effective treatment modalities in promoting wound healing. PSs associates with three main groups of agents: azine dyes, macrocyclic dyes, and metallated derivatives [24–27]. An extensive range of PSs from different groups including azines, porphyrins, phthalocyanines, and chlorophyll

derivatives have been described in eradication of many pathogens such as a variety of bacteria, parasites, viruses, and fungi [22].

Several types of first- and second-generation PSs have been used at minimal doses with laser irradiation performed at wavelengths ranging from 630 to 690 nm, and showed that PDT of acute wounds can lead to an improvement of healing outcomes. Interestingly in one study, the healing of skin flaps after being subjected to ischemia was impaired by PDT treatment, although only one PS (Photofrin) was tested. Further animal model and human wound studies are required to find the main process of enhancement of reepithelization and granulation tissue formation with PDT.

In photodynamic therapy, irradiation of cells with low dosage or small energy may incite proliferation. In using PDT clinically, it is essential to use the suitable doses of both the PS and the activating light source in order to achieve cell death for cancer therapy, or regeneration for wound healing [23]. The newest generations of PSs allowing a faster clearance time of normal tissues are more selective for tumor cells. Although PDT may be nontraumatic but in comparison with nature of lower laser therapy it is almost always traumatic and can cause burns, swelling, pain, and scarring in nearby normal tissue [28].

4.1. Contraindication

Cutaneous hypersensitivity, porphyria, known allergies to porphyrins.

Both Aminolevulinic acid (ALA) and Methyl aminolevulinate (MAL) are in FDA pregnancy category C; reproduction studies have not been performed on animals.

Photodynamic therapy is not approved for use in children.

5. Phototherapy (UV irradiation) and wound healing

New contemporary research shows that controlled UV exposure might have some eventual benefit in wound healing and cutaneous homeostasis. The effectiveness of UV energy in enhancing biological changes depends on the chosen irradiation parameters, with maximal effective wavelength and lowest irradiation level [29]. The main mechanism of phototherapy is related to the depth of penetration. UVA, for example, has the longest wavelength and penetrates to the upper part of dermis in human skin, and UVB only penetrates down to the basal layer; however, UVC only reaches the upper part of the epidermis [30].

UV has bactericidal effect and its radiation to the skin can increase blood flow, producing erythema and epidermal hyperplasia [31]. The induced erythema via vasodilatation and inflammatory response represents the first phase of healing. In addition, UV light irradiation increases cellular proliferation in the stratum corneum [32], which can be a protective mechanism against further sunlight damage.

Although UV protection and antisolar are commonly advised during and after wound healing, it is possible that UV also affects the melanocyte redistribution and prevents the normal cutaneous response to injury [33].

It has been shown that UVC light *per se* could stimulate wound healing. UVC light enhances fibronectin and growth factors release leading to increase healing cascade and wound contraction [34, 35]. UV can promote endothelial cell proliferation [36] and augment epidermal thickness and reepithelialization or desquamation of the leading edge of periulcer epidermal cells [31].

UVC (200–280 nm) has a significant antimicrobial effect and can be used as efficient bactericide agent for treatment of acute wound infections and killing pathogens without undesirable injury to host tissue. UVB (280–315 nm) irradiation to the wound has wound healing stimulating effect and extracorporeal UVB irradiation of blood adds immune system stimulating effects too. Although UVA (315–400 nm) has specific effects on cell biologic events, it has not yet been extensively applied to wound treatment [31].

An interesting study compared the efficacy of phototherapy on wound healing in rats under the normal and high-fat diets and revealed increased wound healing by regulating oxidative stress in rats with metabolic disorders under a high-fat diet [37]. The efficacy of UV therapy on pressure ulcer is not clear due to eventual bias and limited number of trials available for consideration. Further research is recommended to determine possible benefit or drawbacks of this treatment [38].

While low level laser (or light) and photodynamic therapy both have considerable applications in wound care, but penetration of UV light into tissues and its efficacy is restricted. UVC and UVB can damage DNA in host cells and chronic exposure to UV can be carcinogenic. Accordingly, additional study of cellular signaling that occurs after UV exposure of tissue is needed to better indicate the risk and benefits of UV irradiation in wound healing.

5.1. Contraindication of phototherapy

- Childhood
- Pregnancy and breastfeeding (PUVA)
- Immobility or inability to stand unassisted for 10 min or longer
- Very fair skin (skin type 1 and 2, especially PUVA)
- Past excessive exposure to natural sun light or phototherapy
- Immunosuppressive medication
- Photosensitizing creams or medications
- Past skin cancer, especially melanoma [39]

6. Shock wave and wound healing

Although hearing extracorporeal shock wave brings the treatment of urinary stones in the mind [40–43] but it also has some benefits in the treatment of acute and chronic wounds [44]. Shock waves are biphasic high-energy acoustic waves that can be produced by electrohydraulics. Although the exact mechanisms of shock wave therapy are not entirely elucidated, it may harbor eventual immunomodulatory effects, acting by transient micromechanical forces in altering various biologic activities. Shock wave therapy increased expression of macromolecules in wound healing such as VEGF, proliferating cell nuclear antigen, and endothelial nitric oxide synthesis. Because of the considerable experience in using shock wave in the treatment of urolithiasis and other conditions in humans, it appears to be a safe technology. The clinical effect of this technology in various wound types and the particular mechanisms of action are now beginning to be understood. Shock waves may also stimulate sensory nerve fibers and decrease pain. Clinical studies of shock wave therapy in wound healing suggest that many factors such as wound cause, size, and duration may impact response to shock wave therapy. However, the actual administration of shock wave therapy in current clinical studies varies in type (unfocused versus focused). Primary studies suggest that unfocused shock wave therapy is more effective than focused one in the treatment of superficial soft tissue defects yet, without direct comparison between unfocused and focused shock wave therapy in clinical trials to date [33]. Importantly, additional basic science studies along with randomized controlled trials will be necessary to determine the optimal shock wave therapy settings. Currently, the U.S. Food and Drug Administration has approved devices that administer shock wave therapy for the treatment of plantar fasciitis and lateral epicondylitis. Application of such devices for treatment of acute and chronic wounds has not been approved yet. We look forward to future innovation in this field to find out the accurate mechanisms of action and optimal treatment of specific wound types.

6.1. Contraindications

6.1.1. Absolute

Lungs: Treatments must not be performed across or directed to the lungs and heart.

Eyes: Tissue of the eye could be adversely affected by shock wave.

Brain: The destructive forces seen at transitions could damage and destroy brain matter.

Major blood vessels: Both the major blood vessels in the neck and thigh should be avoided to prevent damage and potential catastrophic bleeding.

Major nerves: Superficial major nerves like the brachial plexus, ulna/radial nerve should not be treated directly (treatment around these areas is acceptable just not directly to the nerve).

Open wounds/postsurgical wounds with or without stabilization (glue, stitches, steristrips): Shock wave damages tissues and local circulation. This could lead to degradation of the wound, further bleeding, and delayed healing.

Implanted devices or hormones.

Epiphysis: Open growth plates could potentially be damaged by shock wave either by using settings that create more growth and close them too quickly or by using settings that delay growth.

6.1.2. *Relative*

Genitals; pregnancy; clotting disorders/anticoagulants; joint replacements, certain settings have been used to loosen previously implanted joints ready for a new implant; infection; and cancer.

Corticosteroid injection: Generally people recommend waiting 1 month before application [45].

7. CO₂ laser and wound healing

There are some anecdotal reports of CO₂ laser and wound healing. In an interesting case series two pediatric patients with chronic wounds within scars showed rapid healing with a single-pass treatment by fractionated carbon dioxide (CO₂) laser [46]. In another case series done by Phillips et al., CO₂ laser was used in the treatment of posttraumatic slow healing wounds in three elderly patients. In their report each wound was healed by 60% or greater within 3 weeks [47]. In an interesting article reepithelialization and accelerated wound healing within 4 weeks was reported in one recessive dystrophic epidermolysis bullosa (RDEB) patient with CO₂ laser without blistering or other adverse effects [48]. Although there are no considerable reports of the efficacy of fractional carbon dioxide laser on wound healing, it seems that it has a promising effect on chronic wound without remarkable complications.

7.1. Contraindication

Isotretinoin use within the previous 6 months, active cutaneous bacterial or viral infection in the area to be treated, history of keloid formation or hypertrophic scarring, ongoing ultraviolet exposure, prior radiation therapy to treatment area, collagen vascular disease, chemical peel, and dermabrasion [49].

8. Conclusion

Managing chronic and refractory wounds represents a significant dilemma that physicians are facing and needs invention of new treatment modalities. Wide ranges of the above physical modalities have been introduced and used in wound-healing treatment with different efficacies, but most of them, to some extent, are strange for patients and physicians. Although additional clinical studies must be performed in order to find out the best modalities and the best parameters of wavelength, dosage, and methodology, and especially appropriate treat-

ment protocols, we think these modalities need more attention to be paid and should be kept in mind for treating persistent ulcers.

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