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Guest Editorial

Photobiomodulation in Wound Healing: What Are We Not Considering?

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"In a science so directly practical as that of medicine, and at a time when such a rapid accumulation of facts is taking place, as there is in ours, we are doubly bound to render our knowledge accessible to the whole body of our profession brethren… We would have reform, not revolution; we would preserve the old, and add the new."[1]

Wound treatment is probably one of the most ancient and challenging areas of medicine. The scope of the problem and the social costs of wound treatment become clear when one considers that each year in the United Stateas alone, there are 1,000,000 burn injuries, 50,000,000 elective surgical incisions, 50,000,000 traumatic wounds, and >6,000,000 patients affected with chronic wounds.[2–4]

The guidelines of the official wound healing societies, panels, organizations, and agencies around the world are arrived at by consensus and are evidence based. They are dynamic and continuously updated. The minimal components of these guidelines should include: (1) literature review, (2) definitions, (3) diagnostic criteria, (4) patient stratification, (5) comorbidities, (6) wound bed preparation, (7) specific wound treatment, (8) whole patient treatment, if appropriate, (9) continuing care, and (10) treatment efficacy/outcome measures.[3]

Since the first clinical reports and trials on the role of photobiomodulation (PBM) in wound healing in the late 1980s[5] and 1990s,[6–8] much effort has been made to understand the mechanisms by which PBM effects occur in wound healing. Considerable advances in wound healing have been made in our knowledge of the PBM mechanisms at the basic science and pre-clinical level; however, these findings are not fully reflected in the clinical practice. For those who routinely work with or investigate PBM, the question is not if it works (it works!), nor how it works (there is so much to investigate, but the basic mechanisms are known). The major issue is why, 45 years after Mester's first description,[9] PBM is still not fully incorporated into the guidelines of wound healing societies, or recommended as a routine in wound care services. The answers may vary according to the specialty, country, group, or area of interest, but when one searches for good scientific data in the literature, well-designed clinical trials are, unfortunately, rare.

One point that is not being considered for acute wounds and surgical incisions is that the majority of protocols apply PBM three or more times a week for several weeks, which is unfeasible, especially for health services. Efforts should be made to establish PBM alternative regimens that trigger the expected tissue responses of better-quality healing with the fewest applications possible. This would increase the reliability of PBM as a treatment, as a result of improved patient compliance and reduced costs. For those who manage acute or surgical wounds, there is evidence that PBM applied during trans-surgical time[10] or in the immediate postoperative period, is ideal for triggering a cascade of inflammatory phase events that includes the contraction of the wound, phagocytic chemotaxis and activation, macrophage polarization and differentiation of fibroblasts into myofibroblasts, and collagen organization. All of the classic three phases of wound repair (inflammatory, proliferation, and remodeling) can be modulated with a single early intervention during the inflammatory phase that leads to faster and better wound healing.[10,11] When non-steroidal anti-inflammatory drugs (NSAIDS) are prescribed during the immediate postoperative phase, the same pathological principles are applied, creating an intervention in the initial mediators of inflammation. This is a suppressive intervention that creates no improvement in the final quality of the wound.

The management is completely different when the clinician is facing a chronic wound, as is the pathogenesis of the wound. Most studies still compare heterogeneous clinical wounds. Among the group described as "chronic wounds" (per definition, wounds present for more >3 months) are venous ulcers, pressure ulcers, arterial insufficiency ulcers, diabetic (microangiopathic and neuropathic ulcers), and others. In patients with diabetes, the prevalence of neuropathic, ischemic, and neuroischemic ulcers is 35%, 15%, and 50%, respectively.[12] To design a rigorous clinical trial applying PBM or photodynamic therapy (PDT) in chronic ulcers is not an easy task. In addition to the Consolidated Standards of Reporting Trials (CONSORT) guidelines, the PBM/PDT parameters must be explicitly provided, and an accurate diagnosis of the lesion must be made, including size of the wound, perfusion/ischemia, and infection. Schindl et al. studied PBM in a series of 20 patients with

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recalcitrant ulcers, and found at that time that the irradiation depended upon the diagnosis and size of the lesion.[8] A severe limb ischemia [ankle-brachial index (ABI) <0.7 or a toe pressure of <50 mm Hg] without revascularization leads to rates of amputation of 23% in 12 months.[12] Very few studies using PBM or PDT detail the perfusion of each lesion treated.[13,14] Few studies in the literature describe the habits of the patients (smoking/drinking) and none considered those habits as covariables in the outcome. These are crucial modifying factors of wound healing that should be included in the statistical correlations. Some clinical reports attest that PBM can reduce the size of the lesion. Is this (to reduce the size of the wound) a strong outcome to include PBM in the guidelines? Every professional and patient wants to heal the wound completely. There is an advantage in reducing the wound by 40% compared with controls; however, the individual still has an ulcer, a door of infection, necrosis, and trouble. The desirable outcome is to close the wound in less time with low cost. This statement may seem obvious, but there are studies in the literature attesting that PBM is indicated for chronic wounds because it reduces their size. Studies with longer follow-up are crucial. Chronic ulcers are recurrent. Does PBM prevent or postpone the recurrences? Are the costs of PBM or PDT attractive enough to be included in health services protocols? Rigorous studies on that key question are lacking.

Successful diagnosis and treatment of patients with chronic ulcers involves a multidisciplinary approach that includes: systemic disease control, effective local wound care (PBM), infection control (PDT), pressure relieving strategies, and restoring pulsatile blood flow. If one of these steps is missing, the investigator will not be able to explain the reason that PBM does not show significantly good results. And even if PBM is effective in healing ulcers, it is known that some ulcers simply do not respond to PBM.[15,16] Without the abovementioned information, it will continue to be impossible to explain why these lesions do not respond to PBM. This level of detail must be clarified in the trial description.

Good attempts are being made. Tardivo et al. developed an alghorithim to determine the amputation risk and the best treatment for a diabetic foot, whether it is conservative (including PDT) or surgical.[17] PBM will still be in the group of ''alternative treatments'' indicated for non-healing wounds, if the next clinical trials followed by the wound healing societies and based on these rigorous parameters are not designed. As Virchow stated in 1860, ''disease is not something personal and special, but only a manifestation of life under modified conditions, operating according to the same laws as apply to the living body at all times, from the first moment until death.''[1]

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