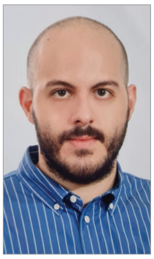
Contribution of photonic therapies to the healing process of chronic wounds: case studies

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Chronic wounds represent an increasing public health issue, since their prevalence is quite high and have caused a major economic problem. In recent years, photonic therapies have emerged as new treatment options for wound healing. A photonic therapy is based on a transfer of energy through photons from a physical system to the wound, which results in observable and measurable modifications in the treated area.
This report describes two different photonic therapies in the care of 10 patients with chronic wounds of various aetiology not responding to standard treatment — blue light photobiomodulation and fluorescence biomodulation.

All types of wounds have the potential of becoming chronic if the complex process of cutaneous healing does not progress normally. Physiological wound healing involves a cascade of factors that are highly regulated, where multiple biological factors interplay (Clark, 1985; Mast and Schultz, 1996; Gurtner et al, 2008; Han and Ceilley, 2017). If the sequence of reparative events is altered due to an underlying disease, infections or metabolic deficiencies, the wound will likely become chronic, causing discomfort for the patient and generating a significant impact to the healthcare system (Han and Ceilley, 2017).

Conventionally, if wounds do not heal after 2 months they are defined as chronic (Adeyi, 2009). Chronic wounds are estimated to exist in 1–2% of the population (Werdin et al, 2008; Nussbaum et al, 2018). The most common chronic wounds are venous leg ulcers, diabetic foot ulcers, pressure ulcers and arterial ulcers. Other soft tissue injuries may also fail to heal, including surgical wounds and traumatic injuries (Werdin et al, 2008; Nussbaum et al, 2018).

Chronic wounds are expensive to treat and costs expand beyond local wound care to indirect social costs, such as pain, reduced, disability, distress and loss of productivity (Ma et al, 2014; Guest et al, 2017; Järbrink et al, 2017; Nussbaum et al, 2018). Due to the aging population and a rising incidence of chronic diseases, prevalence and costs associated with chronic wounds will probably further increase (Järbrink et al, 2017).

The use of light energy for promoting wound healing dates back to the late 19th century, with the use of blue and red light in the treatment of lupus vulgaris (cutaneous tuberculosis). In the late 1960s, low-dose laser treatments began to be used for wound healing.

Only recently has light energy for wound healing been revoluntionised with the introduction of high-efficiency light-emitting diodes (LEDs) due to their affordability, ease of use, and safety (Mosca et al, 2019).

One of the new generation physical therapies used in wound healing is photobiomodulation (PBM), a form of low dose light treatment. This was defined in 2014 by the North American Association for Light Therapy and the World Association for Laser Therapy as the following: "…A form of light treatment that utilizes non-ionizing forms of light sources, including lasers, light emitting diodes (LEDs), and broadband light, in the visible and infrared spectrum, involving a nonthermal process with endogenous chromophores eliciting photophysical (i.e. linear and nonlinear) and photochemical events at various biological scales. This treatment results in beneficial therapeutic outcomes including, but not limited to, the alleviation of pain or inflammation, immunomodulation, and promotion of wound healing and tissue regeneration" (Anders et al, 2015).

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Table 1. Patients treated with Blue Light PBM.					
Patient	Number of ulcers	Aetiology	Comorbodities	Re-epithelialisation achieved	Number of treatments
1	1	Post-traumatic	Diabetes	Healed	3
2	1	Post-traumatic	Diabetes, PAD	Healed	3
3	1	Stump dehiscence	Diabetes, hypertension	97%	21
4	1	Stump dehiscence	Diabetes	69%	10
5	2	Vascular	Hypertension, PAD	89%, 54%	10

Table 2. Patients treated with Fluorescence Biomodulation.					
Patient	Number of ulcers	Aetiology	Comorbodities	Re-epithelialisation achieved	Number of treatments
1	3	Stump dehiscence	Diabetes, PAD	Healed	18
2	1	Stump dehiscence	Diabetes	40%	8
3	1	Vascular	Hypertension	66%	20
4	1	Vasculitic	Diabetes	30%	8
5	1	Post-traumatic	Venous insufficiency	20%	12

The mechanisms of action of blue light photobiomodulation (PBM) are still not completely understood. It is recognised that for low-dose light treatments to have an effect on biological systems, the photons must be absorbed by molecular chromophores or photoacceptors. The candidates as principal photoacceptors are cytochromes involved in the respiratory chain on the mitochondrial membrane. Absorption of photons by cytochromes initiates a biochemical cascade that increase adenosine triphosphate (ATP), generating energy for cell metabolism (Prindeze et al, 2012).

Photobiomodulation has accumulated evidences of a positive action on all phases of wound repair, from inflammatory phase to remodeling phase. These beneficial effects include acceleration of wound healing, cellular and extracellular matrix proliferation, collagen production and granulation tissue formation (Prindeze et al, 2012).

The following is a report of the observations made on 10 patients suffering from ulcers of the lower limbs not responding to standard therapy who were treated with two different photonic therapies: blue light PBM and fluorescence biomodulation (FB). Blue light PBM is based on a direct transfer of energy from a light emitter to the patient, without the use of mediators (chemical additives or medicines), while FB is based on a topical light absorbing molecule gel that is applied to the affected area; an LED light source is used to illuminate the topical product that absorbs light and convert it into dynamic fluorescent energy.

For the purpose of evaluating the effectiveness of the two photonic therapies, the percentage of reepithelialisation achieved over the observation period was measured.

Materials and methods

The blue light PBM therapy was provided through a portable Class IIa Medical Device (EmoLED) equipped with LED sources that emit blue light within the range of 400–430 nm. The effects of blue light reported in preclinical studies and clinical observations are an anticipated transition of inflammation and a faster and better tissue regeneration (Cicchi et al, 2016; Magni et al, 2019; Marchelli et al, 2019; Mosti and Gasperini, 2018). The device does not come into contact with the lesion but must be kept at a distance of 4 cm from the wound bed. It emits blue light for 1 minute on a circular area measuring 5 cm in diameter, providing a uniform power density of 120 mW/cm^2, which corresponds to a fluence of 7.2 J/cm^2. For lesions that measured >5 cm, patients were exposed to multiple, 1-minute applications, in order to cover the entire wound area.

Fluorescence biomodulation was provided through the use of a photo-converter wound gel in conjunction with a LED lamp (LumiHeal). The topical gel contains specific chromophores and when excited with the LED lamp (410 to 470 nm), they release an ultrafast micropulsed emission of photons in the form of fluorescence;

Figure 1a. *Patient 1. Traumatic skin ulcer on the left lower limb. (a, right) Prior to Blue Light PBM therapy. (b, far right) After 3 treatments with Blue Light.*

the fluorescence's energy delivers wavelengths in the spectra of visible light, from 500 to 610 nm. In preclinical and clinical studies a beneficial effect on inflammation and stimulation of the healing process in a physiological manner have been observed (Ferroni et al, 2020; Nikolis et al, 2016; Romanelli et al, 2018; Scapagnini et al, 2019). The topical gel was obtained by mixing two products (vector gel and chromophores) and was applied to the wound bed after the mixture had been prepared. A 2-mm-thick layer of topical gel was applied to the area to be treated. The LED lamp was kept at a distance of 5 cm from the affected area and applied for 5 minutes on a lesion area that measured a maximum of 7.5 cm x 15 cm. Once the application was completed, the activating gel was removed and the skin was cleansed.

The use of both PBM with blue light and FB was complementary to conventional therapies and part of wound bed preparation.

Subjects and setting

Clinical observations were conducted for a maximum period of 4 months on 10 patients (five men and five women; average age 69.7 years) with ulcers of the lower limbs and diverse aetiologies, not responding to standard treatments. These 10 patients formed two groups: one group treated weekly with blue light PBM and the other treated with FB twice weekly. The chronic wounds were: stump dehiscences, post-traumatic ulcers, vascular ulcers and a vasculitic ulcer.

Outcome measures

The outcomes observed over the course of treatment were changes in the size of the wound surface area and level of pain measured by the Visual Analogue Scale. All 10 patients were mentally competent to express their pain using the VAS.

Results

All wounds observed responded to the photonic therapies, recording an increase of granulation tissue in the wound bed with a reduction of the wound's surface.

The wounds treated with blue light PBM had an average size at baseline of 30.5 cm^2 (median 32.4) and reached an average of 88.6% re-epithelialisation. *Table 1* reports results (reepithelialisation achieved) for each patient. A perceived intensity of ≥4 on the VAS was reported in three patients treated with blue light PBM at their first visit, indicative of pain presence. All three patients recorded a significant reduction in pain (93%) at the end of the treatment period. The blue light PBM treatment was well accepted by all five patients.

The wounds treated with FB had an average area at baseline of 30.5 cm^2 (median 25) and reached an average 51.2% reepithelialisation. *Table 2* reports results (reepithelialisation achieved) reached for each patient. A perceived intensity of pain ≥4 on the VAS was reported in all five patients treated with FB at their first visit. For four of these patients an important reduction of the symptom (56%) was recorded, while one patient reported no improvement at the end of the treatment period. No adverse events were recorded; two patients interrupted the therapy due to pain related to the treatment.

The authors outline four interesting cases here, chosen because of the interesting outcomes obtained, given the initial conditions.

The first patient was a 69-year-old male smoker with diabetes and peripheral arterial disease (PAD). The patient had undergone revascularization through angioplasty in both limbs. He presented three post-traumatic iatrogenic ulcers (from rubbing): one in the anterior tibial region of the left leg with a surface area of 48 cm^2 (6 x 8 cm), two in the anterior tibial region of the right leg with a surface area of 6

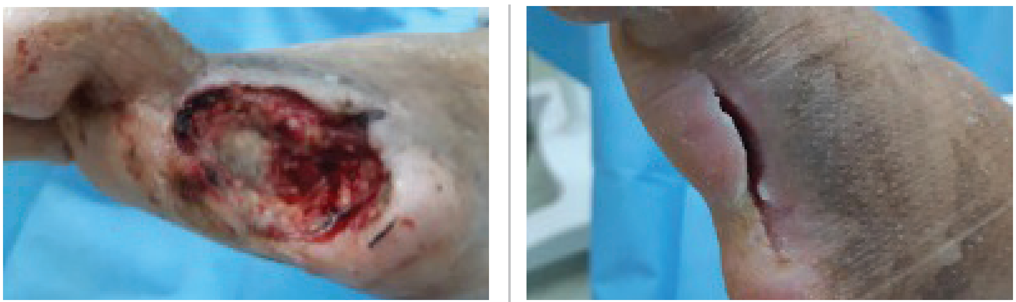

Figure 2. Patient 2. Stump wound dehiscence after toe amputation (fourth and fifth toes) of the left foot. (a, right) Prior to Blue Light PBM therapy. (b, far right) After 21 treatments with Blue Light.

Figure 3. Patient 3. Dehiscence of stump after amputation of first toe on the left foot. (a, right) Prior to Fluorescence Biomodulation therapy. (b, far right) After 18 treatments with Fluorescence Biomodulation.

cm^2 (3 x 3 cm) and 12 cm^2 (4 x 3 cm). The wounds had been present for 12 weeks. Pain before treatment was reported as a 2-point score on the VAS. Healing was fully achieved after 3 treatments with blue light PBM. At the last visit, the wounds showed complete reepithelialisation *[Figure 1]* and the patient rated the pain with 0 points on the VAS.

The second patient was a 60-year-old man with hypertension and type II diabetes mellitus who took insulin on a regular basis. The patient presented a 12 week old wound dehiscence after toe amputation (fourth and fifth toes) of the left foot. The left limb was also previously revascularised through angioplasty.

The wound was quite extensive at baseline, with a surface area of 48 cm^2 (6 x 8 cm) and a lesion depth of 1.8 cm. The wound was characterized by a mixture of fibrin and granulation tissue. Pain assessment confirmed a high discomfort in the patient, with a score of 5 on the VAS. Blue light PBM treatment was performed once a week for 21 weeks. During this period, a significant improvement of the wound was observed, in concurrence with a reduction in lesion size and depth and a revitalization of the wound bed. At the end of the treatment period, a 97% reduction in lesion size and a 90% reduction in lesion depth were observed *[Figure 2]*.

The third patient was a 73-year-old man with diabetes and PAD. The patient presented a wound dehiscence after amputation of the first toe of the left foot. The lesion had been present for 16 weeks. Before treatment, the lesion had a surface area of 18 cm^2 (4.5 x 4 cm), and the related pain was rated 4 on the VAS. After 18 treatments with FB the wound appeared healed, achieving complete re-epithelialization and the patient rated the pain with 0 points on the VAS *[Figure 3]*.

The fourth patient was a 78-year-old woman with diabetes and a vasculitic ulcer in the anterior tibial region of the right lower limb that had been present for 12 weeks. At the baseline visit, the wound had a surface area of 48 cm^2. The patient rated the associated pain with an 8-point score on the VAS.

Treatment was interrupted after the eighth application, since the patient complained of severe pain and a burning sensation. After eight treatments with FB, the lesion size had decreased by approximately 30% and the pain perceived by the patient measured six points on the VAS *[Figure 4]*.

Conclusions

To evaluate the contribution of photonic therapies to the healing process of chronic wounds, blue light PBM or FB was added to standard treatment in the management of unresponsive, hard-to-heal wounds of various aetiology in 10 patients. All wounds observed responded to the photonic therapies: a reduction of the wound size (88.6% with blue light PBM; 51.2% with FB) and pain was achieved with both therapies. However, the authors report anecdotally that blue light PBM therapy proved

Figure 4. Patient 4. Vasculitic ulcer in the anterior tibial region of the right lower limb. (a, right) Prior to Fluorescence Biomodulation (FB) therapy (b, far right) After eight FB treatments, which were discontinued due to patient complaints of pain.

to be easier to administer and better tolerated by patients: the device is handy, the single treatment is fast (only 60 seconds light irradiation on wound surface) and all the patients accepted the therapy. Based on this reported experience, photonic therapies can contribute significantly to the healing of hard-to-heal chronic wounds. WINT

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