EFFECTS OF NIR-LED LIGHT THERAPY ON WOUND HEALING AND NERVE REGENERATION, INFLAMMATORY CONDITIONS, AND ASSOCIATED PROCESSES

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Abbreviations list:
NIR : Near infra red light
LED: Light Emitting Diode
TGF : Transforming growth Factor
KGF : Keratinocyte growth factor

1. Introduction
In this article we would like to share our clinical experience with a novel wound healing device* that is capable of producing near infrared light. The device is portable, battery (rechargeable) powered and suitable for treating chronic wounds. We first give an overview of the literature explaining how NIR light therapy works and in the second part we discuss the clinical results.

* SanoSkin® Photizo® light therapy device

Background of LED near infrared light therapy
Laser light has been widely acclaimed to speed wound healing of ischemic, hypoxic, and infected wounds [1]. Lasers provide low energy stimulation of tissues that results in increased cellular activity during wound healing [2,3]. These activities include collagen production and angiogenesis [4]. Wound healing can be divided in three phases: [i] a substrate is laid down, [ii] cells proliferate, and [iii] there is remodeling of tissue. The data published so far suggests that laser bio-stimulation produces its primary effect during the cell proliferation phase of the wound healing process. It has been demonstrated that mitochondria are receptive to monochromatic near infrared light and that laser light likely increases respiratory metabolism of certain cells [2, 3, 5]. Processes such as fibroblast proliferation, attachment and synthesis of collagen and pro-collagen, growth factor production [including keratinocyte growth factor [KGF], transforming growth factor [TGF] and platelet-derived growth factor [PDGF], macrophage stimulation, lymphocyte stimulation [6] and greater rate of extracellular matrix production have been reported with laser light treatment [7–14]. Animal studies on the enhanced wound healing effect of laser light of low power density have been performed in toads, mice, rats, guinea pigs, and swine [15,16].
Human studies with laser light have demonstrated greater amounts of epithelialization for wound closure and stimulation of skin graft healing [1,9]. Recently, cDNA micro-array technology has been used to investigate the expression of various genes that are induced upon LED treatment and followed through the entire process of healing trying to identify some of the early mid and late events at the molecular level [48].

It has also been found that tissue regenerating genes were significantly up regulated upon LED treatment when compared to the untreated sample [48]. Integrins, nidogen (entactin), laminin, actin, kinesin motor proteins are some of the genes that have been reported to be involved during regeneration process. These are some of the genes that were identified upon gene array experiments with RNA isolated from sponges inserted in the wound site in mice with and without LED treatment.

A wound healing impaired type 2 diabetic mouse model was studied by Whelan et al. (2003). It has been shown that genetically diabetic mice treated with low level laser irradiation demonstrated significantly enhanced wound closure grossly, and improved wound epithelialization, cellular content, granulation tissue formation, collagen deposition, and extensive neovascularization on histological evaluation [21].

In the Whelan study, type 2 diabetic mice with excisional skin wounds were treated with LEDs at individual wavelengths of 680 nm, 730 nm, and 880 nm at 4 J/cm². LED treatment significantly produced increased healing rates, compared to surgical controls.

The biochemical mechanism by which LED enhances the process of wound healing is still under investigation. The current favoured theory is that the infrared light is absorbed by photoreceptors, which then trigger a cascade of reactions in a cell. The major biological photo acceptors in the near-infrared range have been determined to be hemoglobin, myoglobin, and cytochrome oxidase. LED treatment effectively energizes the cells by stimulating their cytochrome oxidase [12, 13] and triggers a cascade of cellular and molecular events that have significant biological benefits. Using gene array technology, it has been shown that a variety of gene families such as basement membrane components are up-regulated by LED when compared to the untreated controls [48].

Expression of basement membrane components occurs during sequential phases of wound healing and angiogenesis. Nidogen is one such protein along with gap junction proteins, actin that were up regulated by LED treatment. Laminin and nidogen transcripts are greatest during the early proliferative-migratory phase of angiogenesis but decrease significantly in
later phases, when vessel maturation and tube formation predominate. There are reports that suggest that wound-induced epithelial cell migration is a finely tuned process that is dependent upon the regulated function and localization of specific laminins and their integrin receptors [22]. Integrin alpha 7 beta 1 is a specific cellular receptor for the basement membrane protein laminin-1, as well as for the laminin isoforms -2 and -4. The alpha 7 subunit is expressed mainly in skeletal and cardiac muscle and has been suggested to be involved in differentiation and migration processes during myogenesis. Both integrins and laminins were among the many up-regulated genes upon LED treatment when compared to the untreated controls. Principal stages of epidermal wound healing in human skin implies a linkage between BM assembly, integrin distribution and the compartment of proliferation competent cells, which in turn determines the onset of differentiation. Thus, apart from the balance of diffusible growth regulators, there is positional control of keratinocytes, largely accomplished by integrin–matrix interactions, which seems to be prerequisite to establishment and maintenance of tissue homeostasis [23]. Homeobox genes are another family of genes, which were altered by LED treatment. Hox 7 and Hox 8 genes are known to play a role for the msh-like family of genes in mesodermal and muscle differentiation and patterning and may act as a key factor up-regulating a variety of proangiogenic stimuli [24]. The formation of new blood vessels from pre-existing blood vessels is thought to be critical for wound repair.

2 HEALING OF BURN WOUNDS USING NIR-LED THERAPY

Al-Watban et al. [2003] determined the effect of polychromatic light-emitting diodes [LED] in burn healing of non-diabetic and streptozotocin-induced diabetic rats [49]. A polychromatic LED light therapy device having a cluster of 25 diodes emitting photons at wavelengths of 510–543, 594–599, 626–639, 640–670, and 842–879 nm with 272-mW output power was used. Burn areas of 1.5 ± .03 cm² were created using a metal rod pre-heated up to 600°C that was applied for 2 sec. Diabetic and non-diabetic rats were randomized into the following treatment groups: control, 5, 10, 20, and 30 J/cm2. Light treatment commenced after burn infliction and was repeated three times per week. Burn areas were measured daily. Burn healing was impaired significantly during diabetes by 246.17%. Polychromatic LED treatment using 5, 10, 20, and 30 J/cm² incident doses influenced healing by 6.85%, 4.93%, 24.18%, and 25.42% respectively in the non-diabetic rats; and 73.87%, 76.77%, 60.92%, and 48.77% respectively in the diabetic rats, relative to their controls.
3 NERVE GROWTH AND REGENERATION

Semaphorins/collapsins have been shown to be markedly increased upon exposure to LED, which may in turn decrease pain [48]. Mouse semaphorin H functions as a chemorepellent to guide or block sensory peripheral nerve ingrowth, most likely via neuropilin as a receptor [25]. With the increase of semaphorin D at the site of the wound, nerve growth would likely be directed to occur around, rather than through the wound area. Numerous studies have shown that pain slows the healing process probably due to CNS-directed recruitment of inflammatory cells to the site of injury and their subsequent release of cytokines/eicosanoids and other mediators.

4 ANTI-INFLAMMATORY EFFECT

It was found by Whelan et al. [2003] that a cluster of calcium binding proteins was altered upon LED treatment. Calpactins are a family of related Ca$_{2+}$-regulated cytoskeletal proteins that were upregulated upon LED treatment. The calpactin I complex is composed of two heavy chain [39 K] and two light chain [11 K] subunits. The heavy chain is a member of a protein family that includes lipocortins, endonexin, and chromobindins, while the light chain is a member of the S100 family [seven distinct members are known]. Many new members of the S-100 genes are known to be associated with cell differentiation, malignant transformation, and cell cycle. The messenger RNA levels of Calpactins have been reported to increase in parallel to the S phase population of cells. Calpactins I and II are proteins that bind Ca$_{2+}$, phospholipids, actin and spectrin; they are also major substrates of oncogene and growth-factor-receptor tyrosine kinases. Transforming growth factor–beta [TGF-beta], a potent regulator of wound healing and scar formation, is thought to have a key role in the response to injury [26]. TSP-1 promotes angiogenesis in the rat aorta model. TSP-1 has a predominant role in the activation of latent TGF-beta in malignant glioma cells [27]. TSP-1 is known to up-regulate the plasminogen activator system through a mechanism involving the activation of TGF-beta 1 [28]. Both TGF beta-1 and TSP-1 were upregulated by 14 days of LED treatment, suggesting they play an important role in the wound healing process.

5 ANTI-APOPTOTIC EFFECT AND DECREASED CELL DEATH

A large number of pro-apoptotic genes along with cytokines and their receptors were down-regulated by LED in the Whelan et al. [2003] study. Activator of apoptosis harakiri [HRK], programmed cell death 1 protein precursor [PDCD-1; PD-1] and RIP were among the many genes involved in apoptosis that were inhibited by LED. Receptor-interacting protein [RIP], a Ser/Thr kinase component of the tumor necrosis factor [TNF] receptor–1 signaling complex,
mediates activation of the nuclear factor kappaB [NFkappaB] pathway. RIP2 has a C-terminal death domain, and RIP2, which has a C-terminal caspase activation and recruitment domain. These cell death-associated genes were downregulated upon LED treatment in the mouse model, which suggests that there is increased proliferation induced by LED.

6. Clinical experiences with LED NIR treatment in chronic wounds.

From literature studies we can learn that in, comparison to general wound dressings, the evidence of the mechanisms on which LED NIR works is more substantial and less accessible for nurses, since it is situated between physics and biochemistry. The NIR light therapy is not new, but the devices that were needed to be used were very expensive and rather user-unfriendly in a typical wound care environment.

In mid-2006 a group of South African engineers made a portable LED NIR light therapy device that was lightweight, easy to operate (pre-programmed treatment protocol buttons) and relatively inexpensive. Once the CE registration was completed we started to test the device in a general hospital and in a community nursing setting in Belgium.

The wounds in the general hospital were mainly venous ulcers that failed to heal with classic wound dressings. In the community nursing setting we treated, apart from venous ulcers, several irradiation burns, diabetic foot ulcers and small burn wounds.

The treatment time per wound is dependent on the size of the wound, but it takes about 2 minutes to treat an area of 4 cm² when a small (100mW) probe is used and when a large probe (400mW) is used over 60 cm² can be treated, also in 2 minutes. The wounds need to be dressed and usually we do continue with the treatment that was started before the NIR light therapy.

So it is not always clear that the light therapy is the only reason why the wounds start to heal, but if the wound dressing (or therapy) is not getting a satisfactory result and the wound starts to heal when NIR light therapy is started then it is clear that the latter is playing an important role in the stage from chronic towards acute healing. In some patients we do not see a significant change in the healing of the wound with the NIR light therapy, but when the patient was suffering from pain before, they do report that the NIR light therapy is acting like a painkiller. We do not know why some chronic wounds do not respond to NIR light therapy, but we do know that NIR light therapy is used as a pain treatment by physiotherapists.
**Results:**

We treated 12 chronic wounds in a *hospital setting* and in 10 patients we found a significant change in healing rate. In short, the chronic wounds turned into acute healing wounds and healed within days while the 2 other wounds slowly healed, but within months. The small time needed for the light therapy in conjunction with the common wound therapy and the simple operation instructions was very well received. The portability of the device was not really an issue in the hospital settings since power plugs are available.

In the *community nursing* setting we treated 16 chronic venous ulcer wounds and here the experiences were similar to the hospital setting. Thirteen wounds healed within weeks, while the remaining 3 were not really responsive to the NIR light therapy. The portability of the device was a very important factor and as most community nurses have short time frames per patient (in Belgium), the short treatment time was necessary.

Four burn wounds (second degree) were treated with NIR light therapy and the main reason for the usage of the NIR light therapy was the pain killing effect the patients were experiencing in this acute wounds. In general the nurses liked the device very much, but they were not used to this kind of wound therapy. Some nurses talked about a “Star Trek” like experience where a simple portable device is healing the wounds.
Case: A 61 year old cancer patient was receiving irradiation therapy after surgical removal of the tumor suffered from irradiation burn wounds. The wound was treated with Wet gauze and once a day Light therapy with the large probe for a total of 8 minutes. The treatment took 20 days to heal the large burn wound completely. The pain the patient was suffering of, was gone due to the light therapy.

Case: A 3 year old chronic venous ulcer closed in 6 days with daily applying light therapy. The wound was treated with a barrier cream and fatty gauze. This clearly demonstrates how light therapy is recharging the exhausted cells leading them to heal the wound.
Case: This chronic difficult to heal venous ulcer started to heal after 3 sessions of 2 minutes light therapy. It is clearly cleaning up and the wound starts to granulate. When a wound responds in days then this a sign that light therapy is making a difference. When it takes longer than a week till the wound shows some improvement then it is very unlikely light therapy will make a difference. on the other hand some people report that even when the wound is not significantly healing, the pain they often have during the night disappears due to the light therapy.

Case: Chronic venous ulcer was not healing with amorphous hydrogel alone, but when treated with the Photizo once a day for 3 minutes (the wound was now covered with a amorphous hydrogel and a foam on top), the wound started to heal. It took 20 days to complete healing when the Photizo therapy was introduced, while the wound was not healing before for over 2.5 months. No compression bandage was used in this patient.
Case: Wound was treated with Photizo 10 months after first problems of non healing occurred. The wound was grafted for the third time and again healing was not going well. The doctors decided to keep the patient in the hospital and treated the wound with Betadine Gel and dressed with a non-woven gauze dressing. The patient was sent home only for the weekend and we asked the surgeons to treat the wound just in the weekend with the Photizo device (2 minutes a day). It took 4 weekends to heal the wound completely.

Conclusion: The Photizo therapy healed the grafted wound in about 8 sessions.

Conclusion
Light therapy is not new, but till recently it was not easy accessible. The overwhelming evidence in the literature about how LED NIR works is a good basis to continue to build up the clinical evidence. There is a need for more clinical proof, but this will come as more doctors and nurses started to use the NIR light therapy in wound care.
REFERENCES


