Effect of NASA light-emitting diode irradiation on molecular changes for wound healing in diabetic mice.

J Clin Laser Med Surg. 2003 Apr;21(2):67-74.

Whelan HT[1], Buchmann EV, Dhokalia A, Kane MP, Whelan NT, Wong-Riley MT, Eells JT, Gould LJ, Hammamieh R, Das R, Jett M.

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The purpose of this study was to assess the changes in gene expression of near-infrared light therapy in a model of impaired wound healing.

Light-Emitting Diodes (LED), originally developed for NASA plant growth experiments in space, show promise for delivering light deep into tissues of the body to promote wound healing and human tissue growth. In this paper we present the effects of LED treatment on wounds in a genetically diabetic mouse model.

Polyvinyl acetal (PVA) sponges were subcutaneously implanted in the dorsum of BKS.Cg-m +/+ Lepr(db) mice. LED treatments were given once daily, and at the sacrifice day, the sponges, incision line and skin over the sponges were harvested and used for RNA extraction. The RNA was subsequently analyzed by cDNA array.

Our studies have revealed certain tissue regenerating genes that were significantly upregulated upon LED treatment when compared to the untreated sample. Integrins, laminin, gap junction proteins, and kinesin superfamily motor proteins are some of the genes involved during regeneration process. These are some of the genes that were identified upon gene array experiments with RNA isolated from sponges from the wound site in mouse with LED treatment.

CONCLUSION:

We believe that the use of NASA light-emitting diodes (LED) for light therapy will greatly enhance the natural wound healing process, and more quickly return the patient to a preinjury/illness level of activity. This work is supported and managed through the Defense Advanced Research Projects Agency (DARPA) and NASA Marshall Space Flight Center-SBIR Program.

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Effect of NASA light-emitting diode irradiation on wound healing.

Whelan HT[1], Smits RL Jr, Buchman EV, Whelan NT, Turner SG, Margolis DA, Cevenini V, Stinson H, Ignatius R, Martin T, Cwiklinski J, Philippi AF, Graf WR, Hodgson B, Gould L, Kane M, Chen G, Caviness J.

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The purpose of this study was to assess the effects of hyperbaric oxygen (HBO) and near-infrared light therapy on wound healing.

Light-emitting diodes (LED), originally developed for NASA plant growth experiments in space show promise for delivering light deep into tissues of the body to promote wound healing and human tissue growth. In this paper, we review and present our new data of LED treatment on cells grown in culture, on ischemic and diabetic wounds in rat models, and on acute and chronic wounds in humans.

In vitro and in vivo (animal and human) studies utilized a variety of LED wavelength, power intensity, and energy density parameters to begin to identify conditions for each biological tissue that are optimal for biostimulation.

LED produced in vitro increases of cell growth of 140-200% in mouse-derived fibroblasts, rat-derived osteoblasts, and rat-derived skeletal muscle cells, and increases in growth of 155-171% of normal human epithelial cells. Wound size decreased up to 36% in conjunction with HBO in ischemic rat models. LED

produced improvement of greater than 40% in musculoskeletal training injuries in Navy SEAL team members, and decreased wound healing time in crew members aboard a U.S. Naval submarine. LED produced a 47% reduction in pain of children suffering from oral mucositis.

CONCLUSION:

We believe that the use of NASA LED for light therapy alone, and in conjunction with hyperbaric oxygen, will greatly enhance the natural wound healing process, and more quickly return the patient to a preinjury/illness level of activity. This work is supported and managed through the NASA Marshall Space Flight Center-SBIR Program.

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Effects of light-emitting diode (led 640nm) on human gingival fibroblasts: a comparative *in vitro* study.

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The light-emitting diodes (LEDs) have been applied in oral surgery for tissue stimulation and wound healing. Several Authors have highlighted that fibroblasts subjected to phototherapy have an increased viability, proliferation, biomodulation of inflammatory cytokines and genes expression. It remains to be determined which are the best irradiation parameters (energy, wavelength, power) for each type of cell in order to obtain the best bio-stimulation. The aim of this study was to investigate the effects of LED irradiation on primary human gingival fibroblast cells (HGF) on DSP, ELN, HAS1, ELANE, HYAL1, RPL13 genes activation using Real Time PCR. These genes activation is directly connected with elastin protein production and HGF functionality.

Human gingival tissue biopsies were obtained from three healthy patients during extraction of teeth. The gingival pieces were fragmented with a scalpel and transferred in culture dishes for allow the cells growth. Human gingival fibroblasts at the second passage were seeded on multiple 6-well plates and were stimulated with three different light-emitting diodes (LEDs) fixture. After irradiation, the cells were trypsinized, harvested and lysed for RNA extraction. Genes expression was quantified using Real Time PCR.

We didn't found significant differences in genes activation of HGF of the three different LEDs. The LED irradiation seems to be directly correlated with the elastin and hyaluronoglucosaminidase 1 genes activation that are directly connected with proteins production and HGF functionality.

HGF show an increased deposition of elastin as well as enhanced expression of collagen type I, which is the main protein related to the synthesis and of the collagen-rich matrix.

The anti-inflammatory mechanism of 635 nm light-emitting-diode irradiation compared with existing COX inhibitors.

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Inhibition of cyclooxygenase (COX) and prostaglandin E(2) (PGE(2)) protects cells against cell injury in specific pathophysiological situations: inflammation and oxidative stress. Although the anti-inflammatory effects have been reported in clinical fields for specific wavelength irradiation during wound healing, the physiological

mechanism has not been clarified yet. The aim of the present study is to investigate the anti-inflammatory mechanism of 635 nm light-emitting-diode (LED) irradiation compared with existing COX inhibitors.

The present study investigated anti-inflammatory effects of 635 nm irradiation on PGE(2) release, COX and phospholipase A(2) (PLA(2)) expression, and reactive oxygen species (ROS) dissociation in arachidonic acid (AA)-treated human gingival fibroblast (hGF). These results were compared with their existing COX inhibitors: indomethacin and ibuprofen. The PGE(2) release was measured by enzyme immunoassay, the COX expression was measured by western blot and reverse transcriptase polymerase chain reaction (RT-PCR), and ROS level was measured by flow cytometry, laser scanning confocal microscope and RT-PCR.

Results showed that 635 nm irradiation and existing COX inhibitors inhibit expression of COX and PGE(2) release. Unlike indomethacin and ibuprofen, 635 nm irradiation leads to a decrease of ROS levels and mRNA expression of cytosolic phospholipase A(2) (cPLA(2)) and secretary phospholipase A(2) (sPLA(2)).

CONCLUSION:

Taken together, 635 nm irradiation, unlike indomethacin and ibuprofen, can directly dissociate the ROS. This inhibits cPLA(2), sPLA(2), and COX expression, and results in the inhibition of PGE(2) release. Thus, we suggest that 635 nm irradiation inhibits PGE(2) synthesis like COX inhibitor and appears to be useful as an anti-inflammatory tool.

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Inflammatory cytokines are suppressed by light-emitting diode irradiation of P. gingivalis LPS-treated human gingival fibroblasts: inflammatory cytokine changes by LED irradiation.

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Human gingival fibroblasts (hGFs) play an important role in the inflammatory reaction to lipopolysaccharide (LPS) from P. gingivalis, which infects periodontal connective tissue. In addition, although light-emitting diode (LED) irradiation has been reported to have biostimulatory effects, including anti-inflammatory activity, the pathological mechanisms of these effects are unclear. This study examined the effects of 635-nm irradiation of P. gingivalis LPS-treated human gingival fibroblasts on inflammatory cytokine profiles and the mitogen-activated protein kinase (MAPK) pathway, which is involved in cytokine production. Gingival fibroblasts treated or not treated with P. gingivalis LPS were irradiated with 635-nm LED light, and cytokine profiles in the supernatant were assessed using a human inflammation antibody array. Expression of cyclooxyginase-2 (COX-2) protein and phosphorylation of extracellular signal-regulated kinase (ERK 1/2), p38, and c-Jun-N-terminal kinase (JNK) were assessed by Western-blot analysis to determine the effects on the MAPK pathway, and prostaglandin E(2) (PGE(2)) in the supernatant was measured using an enzyme-linked immunoassay. COX-2 protein expression and PGE(2) production were significantly increased in the LPS-treated group and decreased by LED irradiation. LPS treatment of gingival fibroblasts led to the increased release of the pro-inflammatory-related cytokines interleukin-6 (IL-6) and IL-8, whereas LED irradiation inhibited their release. Analysis of MAPK signal transduction revealed a considerable decrease in p38 phosphorylation in response to 635-nm radiation either in the presence or absence of LPS. In addition, 635-nm LED irradiation significantly promoted JNK phosphorylation in the presence of LPS. LED irradiation can inhibit activation of pro-inflammatory cytokines, mediate the MAPK signaling pathway, and may be clinically useful as an anti-inflammatory tool.

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Clinical and experimental applications of NIR-LED photobiomodulation.

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Desmet KD[1], Paz DA, Corry JJ, Eells JT, Wong-Riley MT, Henry MM, Buchmann EV, Connelly MP, Dovi JV, Liang HL, Henshel DS, Yeager RL, Millsap DS, Lim J, Gould LJ, Das R, Jett M, Hodgson BD, Margolis D, Whelan HT.

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This review presents current research on the use of far-red to near-infrared (NIR) light treatment in various in vitro and in vivo models. Low-intensity light therapy, commonly referred to as "photobiomodulation," uses light in the far-red to near-infrared region of the spectrum (630-1000 nm) and modulates numerous cellular functions. Positive effects of NIR-light-emitting diode (LED) light treatment include acceleration of wound healing, improved recovery from ischemic injury of the heart, and attenuated degeneration of injured optic nerves by improving mitochondrial energy metabolism and production. Various in vitro and in vivo models of mitochondrial dysfunction were treated with a variety of wavelengths of NIR-LED light. These studies were performed to determine the effect of NIR-LED light treatment on physiologic and pathologic processes. NIRLED light treatment stimulates the photoacceptor cytochrome c oxidase, resulting in increased energy metabolism and production. NIR-LED light treatment accelerates wound healing in ischemic rat and murine diabetic wound healing models, attenuates the retinotoxic effects of methanol-derived formic acid in rat models, and attenuates the developmental toxicity of dioxin in chicken embryos. Furthermore, NIR-LED light treatment prevents the development of oral mucositis in pediatric bone marrow transplant patients. The experimental results demonstrate that NIR-LED light treatment stimulates mitochondrial oxidative metabolism in vitro, and accelerates cell and tissue repair in vivo. NIR-LED light represents a novel, noninvasive, therapeutic intervention for the treatment of numerous diseases linked to mitochondrial dysfunction.

Effects of low-power light therapy on wound healing: LASER x LED.

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Several studies demonstrate the benefits of low-power light therapy on wound healing. However, the use of LED as a therapeutic resource remains controversial. There are questions regarding the equality or not of biological effects promoted by LED and LASER. One objective of this review was to determine the biological effects that support the use of LED on wound healing. Another objective was to identify LED´s parameters for the treatment of wounds. The biological effects and parameters of LED will be compared to those of LASER. Literature was obtained from online databases such as Medline, PubMed, Science Direct and Scielo. The search was restricted to studies published in English and Portuguese from 1992 to 2012. Sixty-eight studies in vitro and in animals were analyzed. LED and LASER promote similar biological effects, such as decrease of inflammatory cells, increased fibroblast proliferation, stimulation of angiogenesis, granulation tissue formation and increased synthesis of collagen. The irradiation parameters are also similar between LED and LASER. The biological effects are dependent on irradiation parameters, mainly wavelength and dose. This review elucidates the importance of defining parameters for the use of light devices.

Therapeutic photobiomodulation: nitric oxide and a novel function of mitochondrial cytochrome c oxidase.

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Currently, light therapies are widely used in both human and veterinarian medicine. The application of light to clinical therapeutics includes: photodynamic therapy, used to kill cancer cells; UVA therapies, used to treat a variety of skin diseases; and photobiomodulation, used to promote cell growth and recovery from injury. Photobiomodu-lation uses light emitting diodes (LEDs) or low energy lasers, which emit light in the visible red to near infrared range. Light in this range penetrates tissue reasonably well, lacks the carcinogenic/mutagenic properties of UV light, and acts on an endogenous photoreceptor which likely acts to initiate light-altered signaling pathways. Although early studies identified mitochondrial cytochrome c oxidase as an endogenous photoreceptor for photobiomodulation, the cellular and molecular mechanisms underlying photobiomodulation have not been clear. Three recent findings provide important new insight. First, nitric oxide has been implicated. Second, cytochrome c oxidase, an enzyme known to reduce oxygen to water at the end of the mitochondrial respiratory chain, has been shown to have a new enzymatic activity--the reduction of nitrite to nitric oxide. This nitrite reductase activity is elevated under hypoxic conditions but also occurs under normoxia. And third, low intensity light enhances nitric oxide synthesis by cytochrome c oxidase without altering its ability to reduce oxygen. From these findings, we propose that cytochrome c oxidase functions in photobiomodulation by producing nitric oxide, a signaling molecule which can then function in both intra- and extracellular signaling pathways. We also propose that the effectiveness of photobiomodulation is under the control of tissue oxygen and nitrite levels.

Effect of light-emitting diode (LED) therapy on the development of osteoarthritis (OA) in a rabbit model.

Oshima Y[1], Coutts RD, Badlani NM, Healey RM, Kubo T, Amiel D.

The objective of this study was to evaluate whether light-emitting diodes (LEDs) could be effective in a noninvasive, therapeutic device for the treatment of osteoarthritic (OA) knee joints.

Five weeks following the anterior cruciate ligament transection (ACLT) of mature New Zealand White rabbits, the animal knees were exposed to LED stimulation at intervals of 10 min/day, 5 days/week for 5 weeks in the experimental group (n=7). The device used high intensity red and infrared (IR) LEDs with a total amount of energy delivered to the skin of 2.4 J/cm(2). Animals were sacrificed at 9 weeks postoperatively. Femoral surface gross morphology was evaluated with a modified Outerbridge classification and mRNA expression of catabolic and anabolic markers from femoral condyle cartilage and synovial tissue was assessed using RT-PCR. A control group was harvested 9 weeks following untreated ACLT.

Gross morphometry of the control group showed four Grade II, two Grade III and one Grade IV (average 2.6) condyles macroscopically. The experimental group showed two Grade I and five Grade II (average 1.7) (Table 1). mRNA expression of aggrecan in the cartilage showed no difference between the groups, however type II collagen expression increased in the experimental group compared with control. TNF-α expression was significantly decreased in the experimental group compared to control.

CONCLUSIONS:

There was general preservation of the articular surface and decreased levels of inflammation in the osteoarthritic joints with the application of LED therapy. This may provide potential application as a noninvasive treatment.

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