Review Article

iMedPub Journals
http://journals.imedpub.com

Insights in Neurosurgery
ISSN 2471-9633

2016
Vol. 1 No. 1:3

DOI: 10.21767/2471-9633.10003

Contributions of Near Infrared Light Emitting Diode in Neurosurgery

Manuel Dujovny[1], Erin Morency[2], Onyekachi Ibe[3], Pablo Sosa[4], Fabian Cremaschi[4]

1 Department of Neurosurgery, Wayne State University, Detroit MI, USA
2 School of Nursing, Oakland University, Human Health Building, Rochester MI, USA
3 College of Engineering and Information Science, DeVry University, Southfield MI, USA
4 Department of Neuroscience, Clinical and Surgical Neurology, School of Medicine, National University of Cuyo, Centro Universidad, Mendoza, Argentina

Corresponding author: Manuel Dujovny

manueldujovny@hotmail.com

1906 Long Lake Shores Drive, Bloomfield Hills, MI 48302.

Tel: 248 758-9662
Fax: 248 758-9667

Citation: Dujovny M, Morency E, Ibe O, et al. Contributions of Near Infrared Light Emitting Diode in Neurosurgery. Neurosurg. 2016, 1:1.

Abstract

Background: Since the discovery of laser for the use of clinical therapies in the early 1960s, light therapies has expanded vastly to accommodate light emitting diodes which the wavelength ranges from red to near infrared. Both laser and light emitting diode have shown to be effective with wound healing, inflammation, and neuroprotection where most lesions occur, with both medical and therapeutic qualities. The utility of NIR fluorescence allows for the ability to detect and give reference to the stability of carotid plaques and their microanatomy. Recently, research has begun to look into the therapeutic effects of NIR light on neurodegenerative diseases.

Objective: To demonstrate that the laser and light emitting diode have shown to be effective and therapeutic for the control of wound healing metabolisms and modulation of inflammation. This article focuses on recent literature with new applications for wound healing, inflammation, as well as neurodegenerative diseases. Also discussed is a comparison of near infrared light emitting diodes and low level laser therapies.

Materials and method: We analyzed medical and engineering books, journals, index medicus, PubMed, FDA recommendations, requirements, patents, social media, and anecdotal evidence related to near infrared light therapy, from 1976 through 2015. The manuscript contains 72 pertinent referenced articles after research of over 250articles.

Conclusion: Light therapy has been shown to be an effective coadjutant therapy for many neurosurgical applications. The LED has had technological advancement in the last decade which makes it an excellent option for light therapy. Unlike the laser, LED devices are portable, cost effective, safer, easy to use and has shown to be effective in wound healing and inflammation on the central and peripheral nervous systems.

Keywords: Near infrared; Light emitting diode; Low level laser therapy; Wound healing; Inflammation; Neurosurgery; Neurology

Received: September 30 2015; **Accepted:** January 18, 2016; **Published:** January 25, 2016

Laser research and development has focused on medical uses since the 1960's. Historically, low level lasers (LLL) have been the predominant type of light therapy used, but more recently light emitting diode (LED) has been studied. Results have shown the LED to be effective as a coadjutant treatment for wound healing, inflammation, neurodegenerative disease and pain, including potential for neurosurgical patients. Light emitting diode is a semiconductor light source that uses p n junction which is made of thin heavy layered semiconductor materials. Near infrared (NIR-LED) therapy emits radiation from the near-infrared region of the electromagnetic spectrum, with wavelengths ranging from around 630 nm to 940 nm. William Herschel is credited with the discovery of near-infrared during the early 1800s, while development of industrial uses was not done until the 1950s. Today, NIR radiation is used in night vision goggles, digital cameras, and remote controls for daily activities.

Medical uses of NIR radiation include imaging, molecular oxygen spectroscopy, photobiomodulation, optic thermography, and remote monitoring.

Over the past decade the LED has had various modifications to improve the construction and production of the device that has increased the commercial availability. NIR LEDs were used in NASA research projects in space to assess plant growth and wound healing.

In the past research into wound healing, inflammation, and pain has focused on low level lasers. What research that is available comparing NIR LED and NIR low level laser therapy (LLLT) shows that outcomes between the two are similar. The NIR LED is more superior in the design, mobility, affordability, and usability; these differences cause the need for further research to be completed on NIR LED GaAs as a coadjutant therapy for various medical conditions involving pain, inflammation, neurodegenerative disease and wound healing.

Materials and Method

We analyzed medical and engineering books, journals, index medicus, pubmed, FDA recommendations, requirements, patents, social media, and anecdotal evidence related to near infrared light therapy, from 1976 through 2015. The manuscript contains 72 pertinent referenced articles after research of over 250 articles. We searched the following keywords; near infrared, light emitting diode, low level laser therapy, pain, traumatic brain injury, spinal cord injury, peripheral nerve injury, sports medicine, Parkinson's disease, Alzheimer's disease, cerebrovascular accident, stroke, microsurgical anatomy of the intracranial artery aneurysm, wound healing, inflammation, dental, neurosurgery, rehabilitation, carotid plaque, diabetic ulcer, and cancer. Exclusion criteria included near infrared photodynamic therapy for cancer treatment.

Results and Discussion

This article summarizes recent literature regarding the laser and light contribution to neurosurgery. Evidence of the quality of this equipment support the use of light therapy as a coadjutant therapy in daily life, sports injuries, surgical procedures, and neurodegenerative diseases.

Wound Healing and Inflammation

Wound healing and inflammation are very common due to daily activities, sports, war terrorism, surgical incisions/interventions (such as craniotomies, spinal surgery, carotid endarterectomy artery surgery, or peripheral nerve surgery).The response by the body to these stressors is a predictable series of events, with increased metabolic needs, and many of the body's responses can be improved with the use of NIR LED GaAs.

The initial stage in wound healing is acute inflammation, during this stage the permeability of vascular tissue increases. The increase is in response to a release of chemical mediators, including histamine, interleukin-1 (IL-1), and tumor necrotic factor (TNF) [1]. The migration of polynuclear leukocytes also causes an increase in vascular permeability. Increased leukocyte activity, IL-1, and TNF all are causes of increased inflammation (**Table 1**). The body responds to increases in all of these components by increasing phagolysosomes to the area of injury, thereby increasing the rate of phagocytosis and the risk for damage.

Vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and reactive oxygen species (ROS) also increase during inflammation. This increase is correlated with tissue damage during inflammation.

Arachidonic acid is a pro-inflammatory agent that is associated with leukocytes. When treated with near-infrared light the effectiveness of arachidonic acid is decreased because cyclooxygenase-2, an enzyme needed by arachidonic acid, is decreased [2, 3]. This limits the inflammatory efforts of arachidonic acid.

While arachidonic acid increases inflammation, nitric oxide (NO) is known to decreased inflammation. The effects of NO are to decrease leukocytes in the area and decrease the vascular permeability. When stimulated by NIR light NO levels have increased, showing a decrease in the inflammatory response to injury [4-6].

Acute inflammation will only resolve once the cause is eliminated or removed. If this does not happen then the body will be in a state of chronic inflammation.

One of the first activities of tissue repair and regeneration is the migration of parenchymal cells. These cells will become the functional cells for the repairing organ. Another important aspect

Table 1 Studies related to near infrared light emitting diode therapy and Inflammation [1].

Name	Year	Research	Outcome
Albertini	2007	the effect of LLLT on the COX-2 mRNA	Reduced effect of COX-2 mRNA.
Vasheghani	2008	Helium-neon laser effects on mast cell degranulation	Mast cell number increased during inflammatory and proliferative but decreasing mast cells during remodeling
Sawasaki I	2009	Effect of LLLT on mast cell degranulation	Increased the number of degranulated mast cells in oral mucosa.
Khoshvaghti A	2011	Effect of low-level treatment on mast-cell numbers and degranulation	Decrease total numbers of mast cells
Mesquita-Ferrari RA	2011	Effect of low-level laser therapy (LLLT) on TNF-α and TGF-β	Decreased TNF-α and TGF-β following cryoinjury
Fernandes, KP	2013	Effect of LLLT on interleukin-1	Decreased IL-1β expression

of tissue regeneration is angiogenesis, which is necessary for the long term outcome of the wound. The extracellular matrix is responsible for creating the proteins that will be used for tissue remodeling.

Fibroblasts are most frequently associated with tissue regeneration, because they are responsible for the bulk of the repair. Whelan et al. observed a 140-200% increase in fibroblasts and a 155-171% increase in epithelial cells when stimulated by hyperbaric oxygen LED [7]. For fibroblast proliferation to occur transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF), and insulin growth factor (IGF) must all be present. Several studies have identified the role of NIR light in increasing these growth factors [8-11]. Fibroblasts are responsible for collagen I and III, which are needed for the integrity of the matrix [12-14]. One model of diabetic rats showed increased collagen after NIR LLLT compared to those treated with no light therapy [15].

During periods of healing the energy requirements of cells are increased. The use of near infrared light treatment using 630 nm-940 nm demonstrated that near infrared light emitting diode treatment stimulates mitochondrial oxidative metabolism in vitro which accelerates cell and tissue repair in vivo. Furthermore, near infrared light emitting diode treatment prevents the development of oral mucositis in pediatric bone marrow transplant patients [16]. Hodgson et al. also showed similar effect using NASA near infrared light emitting diodes of 670 nm with power density of 4 joules Cytochrome c oxidase has been reported to be a receptor for some of the beneficial effects of low intensity visible and near-infrared light on cells and tissues [17]. According to Levi et al. visible light has been found to stimulate reactive oxygen species generation both in membrane and cytoplasm. Also in their experiment, fluorescent measurements confirmed the mitochondria to be a target for light-cell interaction which supports their hypothesis that reactive oxygen species are generated in various cellular sites following light illumination [18]. Dixit et al. observed the NIR LED GaAs improve a chronic ulcer on a 18 year old male patient with thalassemia intermedia. They credit the healing of the wound in part to the mitochondria stimulating effects, more specifically the cytochrome system [19].

NIR LED devices have become much more user friendly with advances in technology. They can be the size of older model cellular telephones, but some have been roughly the size of electric toothbrushes. It has been demonstrated that NIR LEDs can penetrate to a depth of approximately 3 cm [20]. The device can be powered by a cord that plugs into an outlet or by AA or AAA batteries. NIR LED devices can have a wavelength between 640-940 nm. All NIR LEDs must be regulated by the FDA and must be considered a type 2 category.

Discussion

Clinical applications

In 2009, there were a reported 3.5 million incidences of traumatic brain injury [21]. After a traumatic brain injury application of NIR LED resulted in decreased brain edema and improved cognitive function in mice and patients [22-25]. With the increase of sports head injuries (football, hockey, soccer, and boxing) the need to identify effective treatments is required. Traumatic brain injuries have created the need for emergency therapies while waiting for long term solutions. Khuman et al. believe that a therapeutic window of 60-80 minutes is clinically relevant for many avenues, including medics on battlefields [26]. Over the past few years the improvement of cognitive function of concussive syndrome in animals and humans has been studied. A clear decrease of cerebral edema in MRIs was found after 21 days in experimental injury of mice with application of NIR LLLT [23]. On the other hand, Khuman et al. observed no difference in brain edema after 24 hours, using the wet-dry method to measure brain water content, compared to controls, although this time period might not have been sufficient enough to see the effect of therapy. Results from this study did show decreased microgliosis 48 hours post-injury, potentially leading to greater modulation of inflammation. Interestingly, cognitive function, especially the memory, did improve [26]. In 2015, Xuan et al. reported increased brain-derived neurotrophic factor (BDNF) and synapsin-1 in different areas of the brain after mice with TBI were treated with LLLT with NIR light [27]. Moreira et al. treated a cryogenic brain injury model to LLLT and results showed decreased levels of tumor necrosis factor- α, interleukin-1β, and interleukin-6 24 hours post injury [28]. Quirk et al. observed a statistical decrease in Bax pro-apoptotic markers and an increase in Bcl-2 anti-apoptotic markers in a TBI rat model with NIR LED treatment [29]. In a fluid percussion TBI model clinical observations resulted in no differences between Red/NIR LED irradiation therapies at 670 nm or 830 nm in regards to motor abilities and forepaw latency, but no histological analysis was done [30]. With the use of NIR light therapy there is potential for improved recovery and a greater chance of returning to normal activities of daily life [31].

NIR invisible light therapy has shown positive results in embolic rabbit models [32]. Lapchak and De Taboada observed increased levels of cortical adenosine-5-triphosphate in an embolic rabbit model after irradiation with 808 nm in continuous and pulsed waves [33]. A study in Germany is under way to investigate the possible neuroprotective and neuroreparatory outcomes of near infrared laser therapy as transcranial laser therapy [34]. According to Konstantinović et al., NIR low level laser therapy may be able to assist in treatment of strokes by reducing cortex stimulation [35].

Recently it has been pointed out that the infiltration of macrophages on the arterial wall of cerebral aneurysms causes an inflammation reaction by the body and significant changes to the process of wound healing, which may potentially lead to an arterial rupture. NIR light is able to influence the position of fibroblasts and collagen after the irradiation process [36, 37]. This can be a potential coadjutant therapy during the preoperative period, where it may assist in improving wound healing on the arterial wall. Further research needs to be done in the laboratory on the effects of NIR LED and if there are positive results double blind randomized trials should follow.

After initial research with the use of NIR LLLT, by Rochkind, the outcome of the patient was improved [38]. Paula et al. treated Wistar rats with LLLT after moderate traumatic spinal cord injury.

Therapy resulted in faster motor growth, greater control over inflammation, and increased levels of nerve tissue at the sight of injury [39]. Wu et al. observed NIR light therapy, applied non-invasively, increased axonal regeneration as well as functional recovery in various spinal cord injuries [40]. Similarly, after photobiomodulation on adult rats with a dorsal hemisection with, the use of 810 nm light, Byrnes et al. observed greater axonal number and functional recovery along with a decrease in immune cell activity [41].

Injury to the peripheral nerves may occur from a multitude of events, including, but not limited to; daily activities, sports, warfare, and terrorism. NIR light therapy may be an appropriate coadjutant therapy for many peripheral nerve injuries. In a study, by Mohammed et al., adult male rabbit peroneal nerves were treated with 901nm diode laser for eight weeks. Compared to controls, the NIR LLLT treated group had greater myelin layers, thicker nerve fibers, and nodes of Ranvier that were clearer. They concluded that the NIR LLLT created significant structural and cellular changes that show NIR LLLT may be beneficial as a coadjutant therapy [42]. Growth factors repair of myelin. In a double-blind randomized study by Rochkind et al. right sciatic nerves in rats were removed and a neurotube was inserted to reconnect the sections with 780 nm laser irradiation for 14 days following. Results showed that myelinated axons were greater and somato-sensory evoked responses were higher in the group with NIR LLLT [43]. Another Rockind et al. randomized double-blind study completed on humans used 780 nm laser irradiation transcutaneously on the injured peripheral nerve for three hours and then on the correlating spinal cord segment for two hours for 21 days. Results showed that motor function 6 months later was statistically better when compared to the placebo group. Recruitment of voluntary muscles was also greater for the NIR LLLT treated group than control [44]. Gomes et al. treated rats, with a right sciatic nerve crush injury, with NIR LLLT. Upon analysis the rats with NIR LLLT had greater mRNA expression of brain derived neurotrophic factor and nerve growth factor [45].

Near infrared imaging

After vascular tissue injury, such as aneurysms, outcomes are not great [46]. Atherosclerosis results, in part, from an increase in macrophages. NIR has been beneficial in identifying carotid plaque inflammation due to the increase in macrophages [47]. Durand et al. found that indocyanine green helped with the analysis of the microsurgical anatomy of aneurysms [48]. Similarly, Dashti et al. identified indocyanine green as useful for the identification of aneurysm anatomic structures, thereby reducing the risk of complications associated with post-operative ischemic events [49]. Endovascular injection of indocyanine green has been significantly helpful in distinguishing the vein of the arteriovenous cerebellopontine angle. Within the posterior fossa surgery the use of the ECG can be an important factor for safety, to not compromise the perforators from distal ICA and the vein of the cerebellpontine angle [50]. NIR Fluorescence has been used to assist in determining areas dense with VEGFR-1 and VEGFR-2 mRNA after incubation with VEGF/Cy5.5, potentially indicating carotid plaque instability [51]. Similarly, after a surgical endarterectomy and incubation with a MMP-sensitive fluorescence probe, Wallis de Vries et al. used NIR fluorescence imaging to detect "hot spots". These areas of high intensity alerted them to locations of high concentrations of MMPs, which leads to greater plaque instability [52]. NIR fluorescence has also been beneficial in adding in identification of brain tumors (personal communication, Dujovny).

During contact and non-contact sports the risk for injury is increased [31]. In the elderly, ataxia is a reason for frequent injury [53]. Whatever the cause of injury, for the most effective results the NIR LED GaAs should be applied to the site of injury right away.

Pain is commonly associated with injury and inflammation. Treatment for pain should begin after a consultation by a physician to recommend the proper course of action. Surgery is frequently reserved as a last resort to control chronic pain; procedures include neurectomy, rhizotomy, ganglectomy, cordotomy, deep brain stimulation, and cingulectomy. Chronic pain is associated with persistent inflammation. Tendinitis occurs because of the continuous inflammation and perpetual microtrauma. Xavier et al. induced tendinitis in rats with the use of collagenase. After treatment with 880 nm NIR LED results showed less inflammatory cells, at the site of injury, as well as decreased inflammatory cytokines; interleukin-1β, interleukin-6, tumor necrotic factor-α, and COX-2 [54]. Leal-Junior et al. completed a double-blind randomized placebo-controlled trail that resulted in decreased pain for patients reporting nonspecific knee pain [55]. Healing effects of muscle pain related to sports has occurred after treatment with NIR LED [56]. Soccer players with sprained ankles were treated with 820 nm NIR LED GaAS therapy along with the traditional therapy of RICE. Results showed decreased swelling after 24 and 48 hours with no associated recurrence [57]. Potential rational for the decrease in pain intensity is the increase in blood flow and tissue repair [58]. It has also been hypothesized that nociceptive inhibition by NIR light is the reason for potentially lower pain levels [59]. These results raise questions about the efficacy of NIR light therapy as a coadjutant therapy for pain involved with tennis elbow, carpel tunnel, frozen shoulder, temporomandibular joint pain, and others. Research into NIR light therapy effects in oncology patients is sparse; however, Mibu et al. reported reduced anorectal pain in oncology patients receiving NIR LED treatment, with only a few incidence of recurrence [60]. Due to the factors involved with inflammation, and the associated pain, treatment with NIR LED therapy should begin as soon as possible after injury. Further research on the effects of NIR LED coadjutant therapy should be considered in part due to the potential risk of pharmaceutical addiction and pharmaceutical incompatibilities.

Neurodegenerative diseases

Lately it has been suggested that the toll like receptors plays an important role in the beginning of many neurodegenerative diseases and neuroinflammation. It is believed that microglia, astrocytes, and oligodendrocytes may all play a role in the initial immune response that may lead to neurodegeneration [61]. Intracranial use of NIR light has demonstrated to have neuroprotective capabilities, without having any toxic side effects [62]. In a study by Trimmer et al. using human transmitochodrial cybrid (cytoplasmic hybrid neuronal cells with mitochondrial DNA from patients with sporadic Parkinson's disease and disease-free controls) results showed that axonal transport times were decreased after treatment with LLLT [63]. Ying et al. observed increased levels of ATP, decreased rate of cell death, and less reactive nitrogen species in animal models after treatment with near infrared light twice daily [64]. Reinhart et al. treated a Parkinson's disease mouse model with 810 nm NIR light. Results from the study showed improved locomotor activity and greater dopaminergic cells compared to mice not treated with NIR light [65]. When mice were dosed with 50 mg/kg of 1-methyl-4-phenyl-1, 2, 3, 6-tetrhydropyridine results after stimulation with 670 nm NIR light on the body showed enough tyrosine hydroylase-positive cells to conclude that indirect NIR stimulation may lead to neuroprotection [66, 67]. NIR LED therapy has been shown to restore axonal transport and NIR LLLT has increased axonal transport in model human dopaminergic neuronal cells [63]. The Mayo clinic found that with tactile deep brain stimulation there was an increase in levels of ADP [68-70].

Alzheimer's disease has been very difficult to research. The number of people with this diagnosis is on the rise. There has been new research with positive outcomes regarding the use of NIR LED therapy. Treatment of a transgenic rat model with Alzheimer's disease has had histological confirmation of the disappearance of amyloid plaques, along with improvement of rat cognition. Purushothuman et al. also observed decreased levels of hyperphosphorylated tau neurofibrillary tangles after use of NIR LED therapy in K3 mice [71]. Sommer et al. irradiated human neuroblastoma cells with 670 nm laser light and treated them with epigallocatechin gallate. Results from this study showed decreased numbers of amyloid-beta aggregates with the dual therapies [72].

Conclusion

NIR light therapy is able to modulate and control wound healing and inflammation. Ample research is available supporting NIR light as a coadjutant therapy for various wound healing, inflammation, and pain circumstances. Advances in NIR light technology has made it more economical and much more versatile due to size. NIR light research needs to include randomized double blind trials. Once more information is available the authors believe that NIR light therapy will be shown as a valuable coadjutant therapy for many neurosurgical patients. Based on our findings in over 250 articles reviewed, there is not enough basic and clinical research to support the use of light therapy on pregnancy, the eye, and children. Further basic and clinical research needs be conducted to understand the effects. We also recommend further basic and clinical research to be conducted to understand the economic viability; maintenance, training, and initial cost, of the near infrared light emitting diode compared to low level laser therapy.

Limitations

This paper was a review of literature from 1976 through 2015, with little data from any governing bodies. Current research is not inclusive of effects on the eye, pregnancy, children, and deeper structures, which may not be feasible due to limitations of the penetration abilities of the device. As stated previously, more randomized double-blind clinical and basic research analysis of the efficacy of this treatment is needed.

Acknowledgement

The authors would like to acknowledge Jeffery Dikin for research and editing.

Conflict of Interests

None to Report

References

1 Onyekachi I, Morency E, Sosa P, Burkow-Heikkinen L (2015) The role of near-infrared light-emitting diode in aging adults related to inflammation. Healthy Aging Research 4: 24.

2 Albertini R, Aimbire F, Villaverde AB, Silva JA Jr, Costa MS (2007) COX-2 mRNA expression decreases in the subplantar muscle of rat paw subjected to carrageenan-induced inflammation after low level laser therapy. Inflamm Res 56: 228-229

3 Pires D, Xavier M, Araújo T, Silva JA Jr, Aimbire F, et al. (2011) Low-level laser therapy (LLLT; 780 nm) acts differently on mRNA expression of anti-and pro-inflammatory mediators in an experimental model of collagenase-induced tendinitis in rats. Laser Med Sci 26: 85-94.

4 Poyton RO, Ball KA (2011) Therapeutic photobiomodulation: nitric oxide and a novel function of mitochondrial cytochrome c oxidase. Doscov Med 11: 154-159.

5 Ball KA, Castello PR, Poyton RO (2011) Low intensity light stimulates nitrate-dependent nitric oxide synthesis but not oxygen consumption by cytochrome c oxidase: Implications for phototherapy. J Photochem Photobiol B 102: 182-191.

6 Mitchell UH, Mack GL (2012) Low-level laser treatment with near-infrared light increases venous nitric oxide levels acutely: a single-blind, randomized clinical trial of efficacy. Am J Phys Med Rehabil 92: 151-156.

7 Whelan HT, Smits RL Jr, Buchman EV, Whelan NT, Turner SG, et al. (2001) Effect of NASA light-emitting diode irradiation on wound healing. J Clin Laser Med Surg 19: 305-314.

8 Moura Júnior Mde J, Arisawa EÂ, Martin AA, de Carvalho JP, da Silva JM, et al. (2014) Effects of low-power LED and therapeutic ultrasound in the tissue healing and inflammation in a tendinitis experimental model in rats. Lasers Med Sci 29: 301-311.

9 Taniguchi D, Dai P, Hojo T, Yamaoka Y, Kubo T, et al. (2009) Low-energy laser irradiation promotes synovial fibroblast proliferation by modulating p15 subcellular localization. Lasers Surg Med 41: 232-239.

10 Vinck EM, Cagnie BJ, Cornelissen MJ, Declercq HA, Cambier DC (2003) Increased fibroblast proliferation induced by light emitting diode and low power laser irradiation. Lasers Med Sci 18: 95-99.

11 Byrnes KR, Barna L, Chenault VM, Waynant RW, Ilev IK, et al. (2004) Photobiomodulation improves cutaneous wound healing in an animal model of type II diabetes. Photomed Laser Surg 22: 281-290.

12 Silveira PC, Silva LA, Freitas TP, Latini A, Pinho RA (2011) Effects of low-power laser irradiation (LPLI) at different wavelengths and doses on oxidative stress and fibrogenesis parameters in an animal model of wound healing. Lasers Med Sci 26: 125-131.

13 Fiório FB, Albertini R, Leal-Junior EC, de Carvalho Pde T (2014) Effect of low-level laser therapy on types I and III collagen and inflammatory cells in rats with induced third-degree burns. Lasers Med Sci 29: 313-319.

14 de Souza TO, Mesquita DA, Ferrari RA, Dos Santos Pinto D Jr, Correa L, et al. (2011) Phototherapy with low-level laser affects the remodeling of types I and III collagen in skeletal muscle repair. Lasers Med Sci 26: 803-814.

15 Maia LG, Alves AV, Bastos TS, Moromizato LS, Lima-Verde IB, et al. (2014) Histological analysis of the periodontal ligament and alveolar bone during dental movement in diabetic rats subjected to low-level laser therapy. J Photochem photobiol B 135: 65-75.

16 Whelan HT, Connelly JF, Hodgson BD, Barbeau L, Post AC, et al. (2002) NASA light-emitting diodes for the prevention of oral mucositis in pediatric bone marrow transplant patients. J Clin Laser Med Surg 20: 319-324.

17 Hodgson BD, Margolis DM, Salzman DE, Eastwood D, Tarima S, et al. (2012) Amelioration of oral mucositis pain by NASA near-infrared light-emitting diodes in bone marrow transplant patients. Support Care Cancer 20: 1405-1415.

18 Santambrogio P, Dusi S, Guaraldo M, Rotundo LI, Broccoli V, et al. (2015) Mitochondrial iron and energetic dysfunction distinguish fibroblasts and induced neurons from pantothenate kinase-associated neurodegeneration patients. Neurobiol Dis.

19 Dixit S, Agrawal PR, Sharma DK, Singh RP (2014) Closure of chronic non healing ankle ulcer with low level laser therapy in a patient presenting with thalassemia intermedia: Case report. Indian J Plast Surg 47: 432-435.

20 Henderson TA, Morries LD (2015) Near-infrared photonic energy penetration: can infrared phototherapy effectively reach the human brain? Neuropsychiatr Dis Treat 11: 2191-2208.

21 Pacifico A, Amyot F, Arciniegas D, Brazaitis MP, Curley K, et al. (2015) A review of the effectiveness of neuroimaging modalities for the detection if traumatic brain injury. J Neurotrauma

22 Dujovny M, Ibe O, Sosa P, Morency E (2014) Near Infrared LED: An emerging technology on the treatment of stroke. J Neurol Stroke 1: 0039.

23 Oron A, Oron U, Streeter J, de Taboada L, Alexandrovich A, et al. (2012) Near infrared transcranial laser therapy applied at various modes to mice following traumatic brain injury significantly reduces long-term neurological deficits. J Neurotrauma 29: 401-407.

24 Naeser MA, Hamblin MR (2015) Traumatic brain injury: a major medical problem that could be treated using transcranial, red/near infrared LED photobiomodulation. Photomed Laser Surg 33: 443-446.

25 Morries LD, Cassano P, Henderson TA (2015) Treatments for traumatic brain injury with emphasis on transcranial near-infrared laser phototherapy. Neuropsychiatr Dis Treat 11: 2159-2175.

26 Khuman J, Zhang J, Park J, Carroll JD, Donahue C, et al. (2012) Low-level laser light therapy improves cognitive deficits and inhibits microglial activation after controlled cortical impact in mice. J Neurotrauma 29: 408-417.

27 Xuan W, Agrawal T, et al. (2015) Low-level laser therapy for traumatic brain injury in mice increases brain derived neurotrophic factor (BDNF) and synaptogenesis. J Biophotonics 8: 502-511.

28 Moreira MS, Velasco IT, Ferreira LS, Ariga SK, Barbeiro DF, et al. (2009) Effect of phototherapy with low intensity laser on local and systemic immunomodulation following focal brain damage in rat. J Photochem Photobiol B 97: 145-151.

29 Quirk BJ, Torbey M, Buchmann E, Verma S, Whelan HT (2012) near-infrared photobiomodulation in an animal model of traumatic brain injury: Improvements and the behavioral and biochemical levels. Photomed Laser Surg 30: 523-529.

30 Giacci MK, Wheeler L, Lovett S, Dishington E, Majda B, et al. (2014) Differential effects of 670 and 830 nm red near infrared irradiation therapy: a comparative study of optic nerve injury, retinal degeneration, traumatic brain and spinal cord injury. PLoS One 9: e104565.

31 Burkow L, Onyekachi I, Sockwell N, Morency E, Sosa P (2014) The use of near infrared light emitting diodes in treating sports-related injuries. Research 1: 1277.

32 Lapchak PA, Han MK, Salgado KF, Streeter J, Zivin JA (2008) Safety profile of transcranial near-infrared laser therapy administered in combination with thrombolytic therapy to embolized rabbits. Stroke 39: 3073-3078.

33 Lapchak PA, De Taboada L (2010) Transcranial near infrared laser treatment (NILT) increases cortical adenosine-5-triphospate (ATP) content following embolic strokes in rabbits. Brain Res 1306: 100-105.

34 Schellinger PD, Köhrmann M (2012) [Near-infrared laser treatment of acute stroke: from bench to bedside]. Nervenarzt 83: 966-974.

35 KonstantinoviÄ‡ LM, JeliÄ‡ MB, JeremiÄ‡ A, StevanoviÄ‡ VB, MilanoviÄ‡ SD, et al. (2013) Transcranial application of near-infrared low-level laser can modulate cortical excitability. Lasers Surg Med 45: 648-653.

36 Ollikainen E, Tulamo R, Frösen J, Lehti S, Honkanen P, et al. (2014) Mast cells, neovascularization, and microhemorrhages are associated with saccular intracranial artery aneurysm wall remodeling. J Neuropathol Exp Neurol 73: 855-864.

37 Turkmani AH, Edwards NJ, Chen PR (2015) The role of inflammation in cerebral aneurysm. Neuroimmunol Neuroinflammation 2: 102-106.

38 Rochkind S, Shainberg A (2013) Protective effect of laser phototherapy on acetylcholine receptors and creatine kinase activity in denervated muscle. Photomed Laser Surg 31: 499-504.

39 Paula AA, Nicolau RA, Lima Mde O, Salgado MA, Cogo JC (2014) "Low-intensity laser therapy effect on the recovery of traumatic spinal cord injury". Lasers Med Sci 29: 1849-1859.

40 Wu X, Dmitriev AE, Cardoso MJ, Viers-Costello AG, Borke RC, et al. (2009) 810 nm Wavelength light: an effective therapy for transected or contused rat spinal cord. Lasers Surg Med 41: 36-41.

41 Byrnes KR, Waynant RW, Ilev IK, Wu X, Barna L, et al. (2005) Light promotes regeneration and functional recovery and alters the immune response after spinal cord injury. Lasers Surg Med 36: 171-185.

42 Mohammed IF, Al-Mustawfi N, Kaka LN (2007) Promotion of regenerative processes in injured peripheral nerve induced by low-level laser therapy. Photomed Laser Surg 25: 107-111.

43 Rochkind S, Leider-Trejo L, Nissan M, Shamir MH, Kharenko O, et al. (2007) efficacy of 780-nm laser phototherapy on peripheral nerrve regeneration after neurotube reconstruction procedure (double-blind randomized study). Photomed Laser Surg 25: 137-143.

44 Rochkind S, Drory V, Alon M, Nissan M, Ouaknine GE (2007) Laser phototherapy (780 nm), a new modality in treatment of ling-term incomplete peripheral nerve injury: a randomized double-blind placebo-controlled study. Photomed Laser Surg 25: 436-442.

45 Gomes LE, Dalmarco EM, André ES (2012) The brain-derived neurotropic factor, nerve growth factor, neurotrophin-3, and induced nitric oxide synthase expression after low-level laser therapy in an axonotmesis experimental model. Photomed Laser Surg 30: 642-647.

46 Amenta PS, Valle E, Dumont AS, Medel R (2015) Inflammation and intracranial aneurysms: mechanisms of initiation, growth, and rupture. Neuroimmunol Neuroinflammation 2: 68-76.

47 Foss CA, Bedja D, Mease RC, Wang H, Kass DA, et al. (2015) Molecular imaging of inflammation in the ApoE -/- mouse model of atherosclerosis with IodoDPA. Biochem Biophys Res Commun 461: 70-75.

48 Durand A, Penchet G, Thines L (2015) Intraoperative monitoring by imaging and electrophysiological techniques during giant intracranial aneurysm surgery. Neurochirugie

49 Dashti R, Laakso A, Niemelä M, Porras M, Hernesniemi (2009) Microscope-integrated near-infrared indocyanine green videoangiography during surgery of intracranial aneurysms: the Helsinki experience. Surg Neurol 71: 543-550.

50 Sosa P, Dujovny M, Onyekachi I, Sockwell N, Cremaschi F, et al. (2015) Microvascular anatomy of the cerebellar parafloccular perforating space. J Neurosurg.

51 Lam MK, Al-Ansari S, van Dam GM, Tio RA, Breek JC, et al. (2013) Single-chain VEGF/Cy5.5 targeting vegf receptors to indicate atherosclerotic plaque instability. Mol Imaging Biol 15: 250-261.

52 Wallis de Vries BM, Hillebrands JL, van Dam GM, Tio RA, de Jong JS, et al. (2009) Images in cardiovascular medicine. Multispectral near-infrared fluorescence molecular imaging of matrix metalloproteinases in a human carotid plaque using a matrix-degrading metalloproteinase-sensitive activatable fluorescent probe. Circulation 119: e534-536.

53 Morency E, Onyekachi I, Sosa P, Cremaschi F, Burkow-Heikkinen L (2015) Home care attitude and expectations: a reflection on suggested guidelines for home care in the U. S. A. Research 2: 1425.

54 Xavier M, David DR, de Souza RA, Arrieiro AN, Miranda H, et al. (2010) Anti-inflammatory effects of low-level light emitting diode therapy on Achilles tendinitis in rats. Lasers Surg Med 42: 553-558.

55 Leal-Junior E, Johnson D, Saltmarche A, Demchak T (2014) Adjunctive use of combination of super-pulsed laser and light-emitting diodes phototherapy on nonspecific knee pain: double-blinded randomized placebo-controlled trial. Lasers Med Sci 29: 1839-1847.

56 Enwemeka CS, Parker JC, Dowdy DS, Harkness EE, Sanford LE, et al. (2004) The efficacy of low-power lasers in tissue repair and pain control: a meta-analysis study. Photomed Laser Surg 22: 323-329.

57 Stergioulas A (2004) Low-level laser treatment can reduce edema in second degree ankle sprains. J Clin Laser Med Surg 22: 125-128.

58 Chou R, Huffman L (2007) Nonpharmacologic therapies for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guidelines. Ann Intern Med 147: 492-504.

59 Hashmi JT, Huang YY, Sharma SK, Kurup DB, De Taboada L, et al. (2010) Effect of pulsing in low-level light therapy. Lasers Surg Med 42: 450-466.

60 Mibu R, Hotokezaka M, Mihara S, Tanaka M (2003) Results of linearly polarized near-infrared irradiation therapy in patients with intractable anorectal pain. Dis Colon Rectum 46: S50-S53.

61 Ahmad S (2015) Neuroinflammation minireview: the role of TLRs in neuroinflammation.

62 Moro C, Massri NE, Torres N, Ratel D, De Jaeger, et al. (2014) Photobiomodulation inside the brain: a novel method of applying near-infrared light intracranially and its impact on dopaminergic cell survival in MPTP-treated mice. J Neurosurg 120: 670-683.

63 Trimmer PA, Schwartz KM, Borland MK, De Taboada L, Streeter J, et al. (2009) Reduced axonal transport in Parkinson's disease cybrid neurites is restored by light therapy. Mol Neurodegener 4: 26.

64 Ying R, Liang HL, Whelan HT, Eells JT, Wong-Riley MT (2008) Pretreatment with near-infrared light via light-emitting diode provides added benefit against rotenone- and MPP+-induced neurotoxicity. Brain Res 1243: 167-173.

65 Reinhart F, Massri NE, Darlot F, Torres N, Johnstone DM, et al. (2015) 810nm near-infrared light offers neuroprotection and improves locomotor activity in MPTP-treated mice. Neurosci Res 92: 86-90.

66 Johnstone DM, Coleman K, Moro C, Torres N, Eells JT, et al. (2014) The potential of light therapy in Parkinson's disease. ChronoPhysiology and Therapy 4: 1-14.

67 Johnstone DM, el Massri N, Moro C, Spana S, Wang XS, et al. (2014) Indirect application of near infrared light induces neuroprotection in a mouse model of parkinsonism - an abscopal neuroprotective effect. Neuroscience 274: 93-101.

68 Lyons MK (2011) Deep brain stimulation: current and future clinical applications. Mayo Clin Proc 86: 662-672.

69 Shukla P, Basu I, Graupe D, Tuninetti D, Slavin KV (2012) A neural network-based design of an on-off adaptive control for Deep Brain Stimulation in movement disorders. Conf Proc IEEE Eng Med Biol Soc 2012: 4140-4143.

70 Graupe D, Tuninetti D, Slavin KV, Basu I (2014) Closed-loop electrochemical feedback system for DBS. J Neurosurg 121: 762-763.

71 Purushothuman S, Johnstone DM, Nandassena C, Mitrofanis J, Stone J (2014) Photobiomodulation with near infrared light mitigates Alzheimer's disease-related pathology in cerebral cortex - evidence from two transgenic mouse models. Alzheimer's Research & Therapy 6: 2.

72 Sommer AP, Bieschke J, Friedrich RP, Zhu D, Wanker EE, et al. (2012) 670 nm laser light and EGCG complementarily reduce amyloid-ß aggregates in human neuroblastoma cells: basis for treatment of Alzheimer's disease? Photomed Laser Surg 30: 54-60.