Contributions of Near Infrared Light Emitting Diode in Neurosurgery

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 250 articles.

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

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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].

<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
<th>Research</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albertini</td>
<td>2007</td>
<td>the effect of LLLT on the COX-2 mRNA</td>
<td>Reduced effect of COX-2 mRNA.</td>
</tr>
<tr>
<td>Vasheghani</td>
<td>2008</td>
<td>Helium-neon laser effects on mast cell</td>
<td>Mast cell number increased during inflammatory and proliferative but decreasing mast cells during remodeling</td>
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<td></td>
<td></td>
<td>degranulation</td>
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<tr>
<td>Sawasaki I</td>
<td>2009</td>
<td>Effect of LLLT on mast cell degranulation</td>
<td>Increased the number of degranulated mast cells in oral mucosa.</td>
</tr>
<tr>
<td>Khoshvaghti A</td>
<td>2011</td>
<td>Effect of low-level treatment on mast-cell</td>
<td>Decrease total numbers of mast cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>numbers and degranulation</td>
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<tr>
<td>Mesquita-Ferrari RA</td>
<td>2011</td>
<td>Effect of low-level laser therapy (LLLT) on</td>
<td>Decreased TNF-α and TGF-β following cryoinjury</td>
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<td></td>
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<td>TNF-α and TGF-β</td>
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</tr>
<tr>
<td>Fernandes, KP</td>
<td>2013</td>
<td>Effect of LLLT on interleukin-1</td>
<td>Decreased IL-1β expression</td>
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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 site 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 coadjuvant 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 coadjuvant therapy [42]. Growth factors repair of myelin. In a double-blind randomized study by Rockkind et al. right sciatic nerves in rats were removed and a neurutation 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 Rockkind 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 cerebellopontine 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, Duży)).

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, ganglecotomy, 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-1ß, interleukin-6, tumor necrotic factor-ß, 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 coadjuvant 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 coadjuvant 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 transmotochoidal
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-tetrahydropyridine results after stimulation with 670 nm NIR light on the body showed enough tyrosine hydroxylase-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 coadjuvant 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 coadjuvant 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.

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Conflict of Interests

None to Report
References


