

Advances in near infrared light emitting diode in sport medicine and the role of oxygen spectroscopy, wound healing and inflammation in neuroscience.

Manuel Dujovny^{1*}, Erin Morency², Onyekachi Ibe¹, Pablo Sosa³, Fabian Cremaschi³, David Dawood⁴

¹Department of Neurosurgery, Department of Electrical Engineering, Wayne State University, MI, USA

²Department of Nursing, Oakland University, MI, USA

³Department of Neurosurgery, University of Cuyo, Argentina

⁴Department of Mechanical Engineering, USA

Abstract

Objective: To update the latest outcomes on the use of near infrared technology in sport medicine and the central nervous system. **Materials and Methods:** A review and analysis of present research on the achievements of Near infrared light emitting diode use in sport medicine and neuroscience was conducted. During the review medical books, journals, anecdotes, social networks, and magazines of current literature on the uses, and instruments, of Near Infrared light emitting diode were analyzed. **Discussion:** The update on Near infrared light emitting diode oxygen spectroscopy and the effects on wound healing, inflammation, neurodegenerative disease, and pain are presented. Current literature does not support major clinical outcome difference between Near infrared light emitting diode laser treatment and Near infrared light emitting diode treatment. The use of the Near infrared light emitting diode has significant differences regarding equipment location, economic benefits, availability, and the opportunity of immediate care and repetition of use at home by the patient's family.

Keywords: Near infrared, Laser, Light emitting diode, Oxygen spectroscopy, Neuroscience, Wound healing, Inflammation.

Accepted on March 29, 2017

Introduction

Near infrared light emitting diode technology has been used for well over 100 years, but it wasn't until the 1950's that medical uses were discovered. Advances in the technology have allowed for increased neurosurgical uses since 1985, and have continued to grow through present day. Near infrared light emitting diode technology has been used in two ways for neurosurgery; it was developed for transcranial cerebral oximetry (TCCO) measurements of oxygen in the brain, as well as being used for wound healing, inflammation, and pain control. In this article we are discussing a brief overview of the achievements of both techniques.

William Herschel is credited with the discovery of Near infrared light emitting diode during the early 19th century. He questioned how heat and light from the sun can pass through different lenses at different rates. This question led to experiments where he used the sun's rays through a prism, thereby separating the white light into the various colors of the color spectrum. Herschel then recorded the temperature of each color, but to his surprise the greatest temperature that he recorded happened outside of the spectrum that was visible, more specifically, just outside of the red color [1]. A great advance for Near infrared light emitting diode light happened during the 20th century, with the development of the laser and the more recent development of the light emitting diode with the interposition of a gallium arsenide (GaAs) crystal. Early uses of the light emitting diode gallium arsenide include space station produce.

Sports medicine and Neurosurgery has been able to use Near infrared light emitting diode technology because of the ability of light, in the range of 360 nm to 940 nm, to penetrate tissue.

After the photons penetrate the scalp, through the skull and then the brain, they continue to travel, in a banana-like shape, because of the greater probability of scatter over absorption [2]. The typical distance these photons travel is about 4 cm, proven during a cadaver analysis [3]. Various theories suggest penetration depth can be influenced by presence of layered structures and the presence of cerebrospinal fluid (CSF) [4,5].

In 1985, after a dinner discussion, a new equipment to analyze the oxygen of the brain was suggested by Mrs. Dujovny to Mr. David Weaver, chief financial officer of Somanetic at the time, to produce an equipment to measure the TCCO. After extensive laboratory research by Dujovny and McCormick, including double blind measurements of the intensive care unit at Henry Ford Hospital, results from this experiment identified Near infrared light emitting diode spectroscopy just as reliable as measured blood oxygen saturation as other methods, with a range of 23% to 99% [6].

An anecdotal memory during this time shares Martinez Coll Jr, a bioengineer, fitting the sensors to his forehead and taking a deep breath. While holding his breath, he and his research partners, were able to observe oxygenation levels in the brain decrease progressively, and it was not until he took another deep breath that the oxygen levels immediately rose. Dujovny and Weaver identified the normal brain oxygenation saturation concentration range to be roughly 82%, which was confirmed using 100 patients with lower back pain [2].

At the University of Illinois, Dujovny was able to prove the value of the 3100 Somanetic unit in patients undergoing cerebral artery catheterization. He showed that a carotid cavernous sinus fistula embolization, with intravascular oxygen concentration monitoring, was beneficial with immediate normalization

of the cerebral oxygen in the ipsilateral hemisphere. He also observed the benefits of oxygen concentration monitoring during a craniotomy with bone defects [7]. Williams et al. observed better monitoring of cerebral oximetry using transcranial cerebral oximetry, during a carotid endarterectomy than with jugular bulb venous oxygen saturation measurements [8]. During balloon occlusion testing, cerebral brain oxygen levels were monitored and evaluated, identifying safety parameters [9]. Taussky et al. compared frontal Near infrared light emitting diode spectroscopy with regional cerebral blood flow on computer tomography (CT) perfusion imaging, and identified a linear correlation with the use of the frontal Near infrared light emitting diode spectroscopy cerebral oxygenation measurements [10]. Along with the ability to identify areas of hematoma related to traumatic brain injuries (TBI) [11], Near infrared light emitting diode therapy has been correlated with increased verbal memory and executive function in traumatic brain injuries associated deficits [12]. Near infrared light emitting diode spectroscopy is beneficial for sports therapy and understanding muscle oxidation and saturation levels, assisting in providing optimum therapeutic strategies [13].

Near infrared light emitting diode spectroscopy also has applications in psychology and psychiatry; this non-invasive technique has been used to study brain substrates of subjective feeling such as sleepiness, as well as aspects of personality and psychiatric disorders. Japanese researchers have completed research with Near infrared light emitting diode spectroscopy using a verbal fluency task of 3 minutes to investigate frontal lobe function [14].

Fukuda study with the use of Near infrared light emitting diode coadjutant therapy concluded that depression had less activation, bipolar depression had delayed activation, and schizophrenia had reduced activation, with re-activation after the task [15]. Another study on the use of animal assisted therapy for patients with affective mood disorders used Near infrared light emitting diode spectroscopy to observe the prefrontal cortex. Results showed increased levels of oxy-Hb during animal assisted therapy, and concluded that further use of animal assisted therapy effectiveness can be evaluated with the use of Near infrared light emitting diode spectroscopy [16].

Watanabe et al. studied the pathophysiology of migraines with the use of Near infrared light emitting diode spectroscopy. Results showed that with the injection of sumatriptan oxy-Hb levels were reduced, which is expected with the onset of pain relief. They also observed a correlation between the changes in oxy-Hb and skin blood flow [17].

Lately, research and clinical analysis of the uses of light therapy is focused on the use of near infrared light emitting diode therapy after injuries since it has shown to have a beneficial effect on wound healing, inflammation and pain.

Sports medicine can benefit from the addition of the Near infrared light emitting diode to current standards of treatment. Treatment with Near infrared light emitting diode has been shown to decrease inflammation and speed the wound healing process [18]. Once study concluded that with the addition of Near infrared light emitting diode therapy, university athletes were able to return to the field sooner after various sprains, strains, and other sports related injury [19].

After injury, inflammation is the first process for wound healing. During this period, the vascular tissue increases in permeability, allowing for chemical mediators, such as histamine, interleukin-1, and tumor necrotic factor to increase in number at the site of injury. This increase in activity at the injury is part of a positive feedback system that, in turn, increases inflammation [20]. With the greater number of cells at the site comes greater need for phagocytes, which increases the potential for damage to the area.

Arachidonic acid, a pro-inflammatory agent, is also increased, because of the increase in leukocytes. Arachidonic acid requires the enzyme cyclooxygenase-2, which has been shown to be decreased after treatment with Near infrared light emitting diode. Nitric oxide (NO) is known to decrease inflammation, and Near infrared light emitting diode therapy studies have shown increases in levels of Nitric oxide after treatment [21-25].

With the increase in sports related traumatic brain injuries, from sports like American football, soccer, boxing, wrestling, hockey, rugby, basketball, ice-skating, weightlifting, cycling, and baseball, violence by humans along with increases in terrorist activities and war, the need to find coadjutant therapies that can be initiated at the onset of injury has increased. Injury to the central nervous system has shown an improvement with the treatment of Near infrared light emitting diode.

After traumatic brain injury treatment with Near infrared light emitting diode laser phototherapy has shown decreased levels of depression, anxiety, headache, and insomnia. The authors concluded that treatment with a Near infrared light emitting diode laser within the range of 810 nm and 980 nm can treat chronic symptoms of traumatic brain injuries [26,27]. Experimentally, treatment of traumatic brain injuries with Near infrared light emitting diode has shown a positive improvement on cerebral edema and metabolic changes in the brain [28,29]. 21 days after injury, Oron et al. observed decreased cerebral edema in mice after treatment with Near infrared light emitting diode low level laser therapy [30]. Khuman et al. observed decreased microgliosis 48 hours after injury, while also observing that cognitive capabilities improved [31]. Naeser et al. researched chronic, mild traumatic head injury, and after treatment with Near infrared light emitting diode therapy all participants showed improvement in at least one of the following; executive function, verbal learning, and memory [32].

Spinal cord injury may also respond with positive outcomes after treatment Near infrared light emitting diode. One study resulted in increased axonal regeneration after treatment with non-invasive Near infrared light emitting diode treatment [33]. Wistar rats were treated with low level laser therapy, after moderate traumatic spinal cord injury. Results from treatment included increased motor growth, less inflammation, and greater nerve tissue [34].

Clinical and experimental analysis by Mohammed et al. have shown that adult male rabbits with peroneal nerve injuries responded with positive outcomes after treatment with low level laser, they concluded that low level laser treatment improved myelin layers, nerve fiber regeneration, and clearer nodes of Ranvier [35]. A randomized double-blind study on humans,

conducted by Rochkind et al. resulted in statistically better motor function after treatment with low level irradiation of 780 nm. They also observed better recruitment of voluntary muscles with the group that received treatment over the control [36].

Current research on the uses of Near infrared light emitting diode light for neurodegenerative diseases has yielded neuroprotective capabilities, with current literature showing no toxic side effects [37]. In a Parkinson's disease model with mice treated with 810 nm Near infrared light emitting diode, the results showed greater ability for controlled locomotor activity, as well as more dopaminergic cells [38]. After treatment with Near infrared light emitting diode, k3 mice had decreased hyper phosphorylated tau neurofibrillary tangles [39].

Near infrared light emitting diode light treatments can also be used as a coadjutant therapy for pain after injury, which can occur after injury from daily life events, warfare, terrorism, and sports events. In a double-blind randomized placebo-controlled trial, Leal et al. observed decreased pain after Near infrared light emitting diode treatment for nonspecific knee pain [40]. Two potential theories for the reason that Near infrared light emitting diode light therapy reduces pain includes the effect of increased blood flow, tissue repair, and decrease of inflammation, as well as the inhibition of nociceptive receptors after treatment with Near infrared light emitting diode [41,42]. After ankle injury, treatment with Near infrared light emitting diode therapy has resulted in decreased edema and pain, when used as a coadjutant therapy to the traditional method of RICE [43].

Although the laser and the light emitting diode gallium arsenide (GaAs) can both produce the Near infrared light emitting diode beam for therapy a significant difference can be found regarding the modus operandi. First the laser needs to be in a hospital or office space, while the light emitting diode can be used just about anywhere, increasing mobility and accessibility by the patient's family to provide care at home or wherever else meets the needs. Most lasers require training, while the light emitting diode can be used after review of a user's guide. Lasers are much more expensive to use than a light emitting diode. Light emitting diode also allow for immediate use after an injury as a proactive measure for the inflammatory process [44]. The light emitting diode should be used as a coadjutant therapy and should never be used as a stand-alone treatment.

A major complaint post-injury is the pain associated with injury and healing. The use of Near infrared light emitting diode coadjutant therapy has been associated with reduced complaints of pain during the healing process [45]. Phototherapy has been hypothesized to be able to block transmission of pain via the nerve pathway [46]. The use of light therapy has been hypothesized to be able to interrupt the sympathetic response, managing pain levels [47]. Headaches associated with temporomandibular joint pain have had a positive effect after treatment with low level laser therapy, hypothesized to be because of better blood flow regulation [48]. Another study used red and infrared light emitting diode therapy to treat pain associated with temporomandibular joint pain. They concluded that this light emitting diode therapy reduced associated pain and that it might be an alternative for low level laser therapy [49].

Conclusion

Near infrared light emitting diode therapy has been shown to be beneficial in many ways as a coadjutant therapy. The uses of Near infrared light emitting diode spectroscopy for diagnostic purposes has been established. More recently, research into Near infrared light emitting diode therapy has identified positive outcomes for psychosocial issues, wound healing, pain, inflammation, and others. The mobility and relative ease of using Near infrared light emitting diode therapies makes it a perfect tool to engage patients as a part of their healing process. To identify the best uses for this therapy more double-blind, randomized control trials should be completed.

References

1. Lequeux J. François Arago: A 19th century French humanist and pioneer in Astrophysics. Switzerland: Springer International Publishing, 2008.
2. Misra M, Stark J, Dujovny M, et al. Transcranial cerebral oximetry in random normal subjects. *Neurol Res.* 1998;20:137-41.
3. Buge F, Chiavassa S, Hervé C, et al. Preclinical evaluation of intraoperative low-energy photon radiotherapy using spherical applicators in locally advanced prostate cancer. *Front Oncol.* 2015;5:204.
4. Okada E, Delpy DT. Near-infrared light propagation in an adult head model. I. Modeling of low-level scattering in the cerebrospinal fluid layer. *Appl Opt.* 2003;42:2906-14.
5. Okada E, Delpy DT. Near-infrared light propagation in an adult head model. II. Effect of superficial tissue thickness in the sensitivity of the near-infrared spectroscopy signal. *Appl Opt.* 2003;42:2914-22.
6. McCormick PW, Stewart M, Goetting MG, et al. Non-invasive cerebral optical spectroscopy for monitoring cerebral oxygen delivery and hemodynamics. *Crit Care Med.* 1991;19:89-7.
7. Dujovny M, Ausman JI, Stoddart H, et al. Somanetics INVOS 3100 cerebral oximeter. *Neurosurgery.* 1995;37:160.
8. Williams IM, Picton A, Farrell A, et al. Light-reflective cerebral oximetry and jugular bulb venous oxygen saturation during carotid endarterectomy. *Br J Surg.* 1994;81:1291-5.
9. Agner C, Dujovny M. Historical evolution of neuroendovascular surgery of intracranial aneurysms: From coils to polymers. *Neurol Res.* 2009;31(6):632-7.
10. Tausky P, O'Neal B, Daugherty WP, et al. Validation of frontal near-infrared spectroscopy as noninvasive bedside monitoring for regional cerebral blood flow in brain-injured patients. *Neurosurg Focus.* 2012;32(2):E2.
11. Sen AN, Gopinath SP, Robertson CS. Clinical application of near-infrared spectroscopy in patients with traumatic brain injury: A review of the progress of the field. *Neurophotonics* 2016;3(3):031409.
12. Naeser MA, Martin PI, Ho MD, et al. Transcranial, red/near-infrared light-emitting diode therapy to improve cognition

- in chronic traumatic brain injury. *Photomed Laser Surg.* 2016;34(12):610-26.
13. Quaresima V, Lepanto R, Ferrari M. The use of near infrared spectroscopy in sports medicine. *J Sports Med Phys Fit.* 2003;43(1):1-13.
 14. Robinson G, Shallice T, Bozzali M, et al. The differing roles of the frontal cortex in fluency tests. *Brain.* 2012;135(7):2202-14.
 15. Fukuda M. Near-infrared spectroscopy in psychiatry. *Brain Nerve.* 2012;64(2):175-83.
 16. Aoki J, Iwahashi K, Ishigooka J, et al. Evaluation of cerebral activity in the prefrontal cortex in mood (affective) disorders during animal-assisted therapy (AAT) by near-infrared spectroscopy (NIRS): A pilot study. *Int J Psychiatry Clin Pract.* 2012;16(3):205-13.
 17. Watanabe Y, Tanaka H, Takashima R, et al. Monitoring cerebral blood volume changes during migraine attack by using near-infrared spectroscopy. *Rinsho Shinkeigaku.* 2012;52(11):1009-11.
 18. Burkow L, Onyekachi I, Sockwell N, et al. The use of near infrared light emitting diodes in treating sports-related injuries. *Research.* 2014;1:1277.
 19. Onyekachi I, Morency E, Sosa P, et al. The role of near-infrared light-emitting diode in aging adults related to inflammation. *Health Aging Res.* 2015;4:24.
 20. Albertini R, Aimbire F, Villaverde AB, et al. COX-2 mRNA expression decreases in the subplantar muscle of rat paw subjected to carrageenan-induced inflammation after low level laser therapy. *Inflamm Res.* 2007;56(6):228-9.
 21. Pires D, Xavier M, Araújo T, et al. 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.* 2011;26(1):85-4.
 22. Poyton RO, Ball KA. Therapeutic photobiomodulation: Nitric oxide and a novel function of mitochondrial cytochrome c oxidase. *Doscov Med.* 2011;11(57):154-9.
 23. Ball KA, Castello PR, Poyton RO. Low intensity light stimulates nitrate-dependent nitric oxide synthesis but not oxygen consumption by cytochrome c oxidase: Implications for phototherapy. *J Photochem Photobiol B* 2011;102(3):182-1.
 24. Mitchell UH, Mack GL. 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* 2012;92(2):151-6.
 25. Henderson TA, Morris LD. SPECT perfusion imaging demonstrates improvement of traumatic brain injury with transcranial near-infrared laser phototherapy. *Adv Mind body Med.* 2015;29(4):27-3.
 26. Morris LD, Cassano P, Henderson TA. Treatments for traumatic brain injury with emphasis on transcranial near-infrared laser phototherapy. *Neuropsychiatr Dis Treat.* 2015;11:2159-75.
 27. Dujovny M, Ibe O, Sosa P, et al. Near Infrared LED: An emerging technology on the treatment of stroke. *J Neurol Stroke.* 2014;1(6):0039.
 28. Naeser MA, Hamblin MR. Traumatic brain injury: A major medical problem that could be treated using transcranial, red/near infrared LED photo biomodulation. *Photomed Laser Surg.* 2015;33(9):443-446.
 29. Oron A, Oron U, Streeter J, et al. Near infrared transcranial laser therapy applied at various modes to mice following traumatic brain injury significantly reduces long-term neurological deficits. *J Neurotrauma.* 2012;29:401-7.
 30. Khuman J, Zhang J, Park J, et al. Low-level laser light therapy improves cognitive deficits and inhibits microglial activation after controlled cortical impact in mice. *J Neurotrauma.* 2012;29(2):408-17.
 31. Naeser MA, Zafonte R, Kregel MH, et al. Significant improvements in cognitive performance post-transcranial, red/near-infrared LED treatments in chronic, mild TBI: Open-protocol study. *J Neurotrauma.* 2014;31:1008-17.
 32. Wu X, Dmitriev A, Cardoso M, et al. 810 nm wavelength light: An effective therapy for transected or contused rat spinal cord. *Lasers Surg Med.* 2009;41:36-1.
 33. Paula A, Nicolau R, Lima M, et al. Low-intensity laser therapy effect on the recovery of traumatic spinal cord injury. *Lasers Med Sci.* 2014;29:1849-59.
 34. Mohammed IF, Al-Mustawfi N, Kaka LN. Promotion of regenerative processes in injured peripheral nerve induced by low-level laser therapy. *Photomed Laser Surg.* 2007;25(2):107-11.
 35. Rochkind S, Drory V, Alon M, et al. Laser phototherapy (780 nm), a new modality in treatment of long-term incomplete peripheral nerve injury: A randomized double-blind placebo-controlled study. *Photomed Laser Surg.* 2007;25(5):436-42.
 36. Moro C, Massri NE, Torres N, et al. Photo biomodulation 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.* 2014;120(3):670-83.
 37. Reinhart F, Massri NE, Darlot F, et al. 810 nm near-infrared light offers neuroprotection and improves locomotor activity in MPTP-treated mice. *Neurosci Res.* 2015;92:86-90.
 38. Purushothuman S, Johnstone DM, Nandassena C, et al. Photo biomodulation with near infrared light mitigates Alzheimer's disease-related pathology in cerebral cortex-evidence from two transgenic mouse models. *Alzheimer's Res Ther.* 2014;6:2.
 39. Leal-Junior E, Johnson D, Saltmarche A, et al. 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.* 2014;29:1839-47.
40. Chou R, Huffman L. 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.* 2007;147:492-04.
 41. Hashmi JT, Huang Y, Sharma SK, et al. Effect of pulsing in low-level light therapy. *Lasers Surg Med.* 2010;42(6):450-66.
 42. Stergioulas A. Low-level laser treatment can reduce edema in second degree ankle sprains. *J Clin Laser Med Surg.* 2004;22(2):125-8.
 43. Holanda VM, Chavantes MC, Wu X, et al. The mechanistic basis for photo biomodulation therapy of neuropathic pain by near infrared laser light. *Lasers Surg Med,* 2017; epub ahead of print.
 44. Foley J, Vasily DB, Bradle J, et al. 830 nm light-emitting diode (LED) phototherapy significantly reduced return-to-play in injured university athletes: A pilot study. *Laser Ther.* 2016;25(1):35-41.
 45. Morency E, Dujovny M, Ibe O, et al. The role of the near-infrared light-emitting diode in dental. *Oral Surg.* 2015;1(4).
 46. Liao CD, Rau CL, Liou TH, et al. Effects of linearly polarized near-infrared irradiation near the stellate ganglion region on pain and heart rate variability in patients with neuropathic pain. *Pain Med.* 2016; epub ahead of print.
 47. Tomaz de Magalhães M, Núñez SC, et al. Light therapy modulated serotonin levels and blood flow in women with headache. A preliminary study. *Exp Biol Med.* 2016;241(1):40-5.
 48. Panhoca VH, Lizarelli Rde F, Nunez SC, et al. Comparative clinical study of light analgesic effect on temporomandibular disorder (TMD) using red and infrared LED therapy. *Lasers Med Sci.* 2015;30(2):815-22.

***Correspondence to:**

Manuel Dujovny
1906 Long Lake Shore Drive
Bloomfield Hills, MI 48302
USA
Tel: (248) 758-9662
Fax: (248) 758-9667
E-mail: manuedujovny@hotmail.com