Mini Review
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The use of Low Level Laser Therapy (LLLT) for musculoskeletal pain

Abstract

Pain is the most common reason for physician consultation in the United States. One out of three Americans is affected by chronic pain annually. The number one reason for missed work or school days is musculoskeletal pain. Currently accepted therapies consist of non-steroidal anti-inflammatory drugs, steroid injections, opiate pain medications and surgery, each of which carries their own specific risk profiles. What is needed are effective treatments for pain which have an acceptably low risk-profile. For over forty years, low level laser (light) therapy (LLLT) and LED therapy (also known as photobiomodulation) has been shown to reduce inflammation and edema, induce analgesia, and promote healing in a range of musculoskeletal pathologies. The purpose of this paper is to review the use of LLLT for pain, the biochemical mechanisms of action, the dose response curves, and how LLLT may be employed by orthopedic surgeons to improve outcomes and reduce adverse events.

With the predicted epidemic of chronic pain in developed countries, it is imperative to validate cost-effective and safe techniques for managing painful conditions which would allow people to live active and productive lives. Moreover the acceptance of LLLT (which is currently being used by many specialties around the world) into the armamentarium of the American health care provider would allow for additional treatment options for patients. A new cost-effective therapy for pain could elevate quality of life while reducing financial strains.

Keywords: musculoskeletal, pain, low level laser therapy, photobiomodulation, injury repair

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Abbreviations: LED, Light Emitting Diodes; LLLT, Low Level Laser Therapy; PBM, Photobiomodulation; NO, Nitric Oxide; ATP, Adenosine Triphosphate; ROS, Reactive Oxygen Species; MMP, Membrane Potential

Introduction

Musculoskeletal pain affects 116 million Americans annually at a cost of $635 billion a year in medical bills, lost productivity and missed work or schoo.[1,2] All therapeutic treatments have their benefits, but also possess different side effects, risks and or complications. The current treatment for musculoskeletal pain includes modalities, immobilization, medications, chiropractic care, physical therapy, behavioral management, injections and/or surgery. These standard therapies have their particular associated risks/side effect profiles including peptic ulcers/gastric bleeding,[3] systemic effects (cardiovascular),[4] infections (including epidural abscess),[5] narcotic dependency/addiction,[6] deformities, neurologic deficits, and surgical complications.[7] The natural history of chronic pain is one of increasing dysfunction, impairment and possible disability.

The definition of pain by the "International Association for the Study of Pain" states: "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".[8] Withdrawal of the painful stimulus usually resolves pain promptly. Sometimes however, pain persists in spite of removal of the stimulus and even after healing of the body. Pain can also arise in the absence of any stimulus, disease or injury. Acute pain is considered to last less than thirty days, while chronic pain is of more than six months duration or as "pain that extends beyond the expected period of healing". There are three different types of pain; nociceptive, neuropathic and central. The current medical treatment of pain or analgesics is directed at various steps of the pain pathways (Figure 1). Clinically, low level laser therapy (LLLT) can treat nociceptive[9] and neuropathic pain,[10] while central pain has not yet been proven to be responsive to LLLT.

What is LLLT?

Low Level Laser Therapy (LLLT) sometimes known as Low Level Light Therapy or Photobiomodulation (PBM) is a low intensity light therapy. The effect is photochemical not thermal. The light triggers biochemical changes within cells and can be compared to the process of photosynthesis in plants, where the photons are absorbed by cellular photoreceptors and triggers chemical changes.

History of LLLT

In 1903, Dr. Nils Finsen was awarded a Nobel Prize for his contribution to the treatment of diseases, especially lupus vulgaris, with concentrated light radiation.[11] In 1960, Professor Maiman TH[12] built the first working red ruby laser,[12] but it was not until 1967 when Mester E et al.[13,14] was able to demonstrate the phenomenon of "laser bio stimulation".[13,14] In 1999, Whelan H et al.[15] presented his work on the medical applications of light emitting diodes (LED) for use on the

NASA space station.[15] Subsequently over 400 Phase III randomized, double-blind, placebo-controlled trials have been published, with over 4000 laboratory studies of LLLT. (Pubmed.gov)

A laser is a device that generates light through a process of optical amplification based on the stimulated emission of electromagnetic radiation. There are four main classes of lasers as defined by the International Engineering Consortium (IEC standard 60825.) These classes indicate potential danger the radiation is to the eye.

1. Class 1/1M– CD player
2. Class 2/2M– laser pointer
3. Class 3R/3B – LLLT and CD and DVD writers
4. Class 4 – Surgical laser

LLLT is the application of light (usually a low powered laser or LED typically power range of (10mW-500mW). Light with a wavelength in the red to near infrared region of the spectrum (660nm-905nm), is generally employed because these wavelengths have the ability to penetrate skin, and soft/hard tissues (Figure 2) and are proven in clinical trials to have a good effect on pain, inflammation and tissue repair. The power density (irradiance) is usually between 5W/cm2 and is applied to an injury or to a painful site for 30-60 seconds a few times a week for several weeks. The result is a reduction of inflammation, pain relief and accelerated tissue regeneration. In most cases the lasers/LEDs used for LLLT emit a divergent beam (not focused or collimated) because collimation is lost in tissue, but as a consequence ocular risks are also diminished over distance.

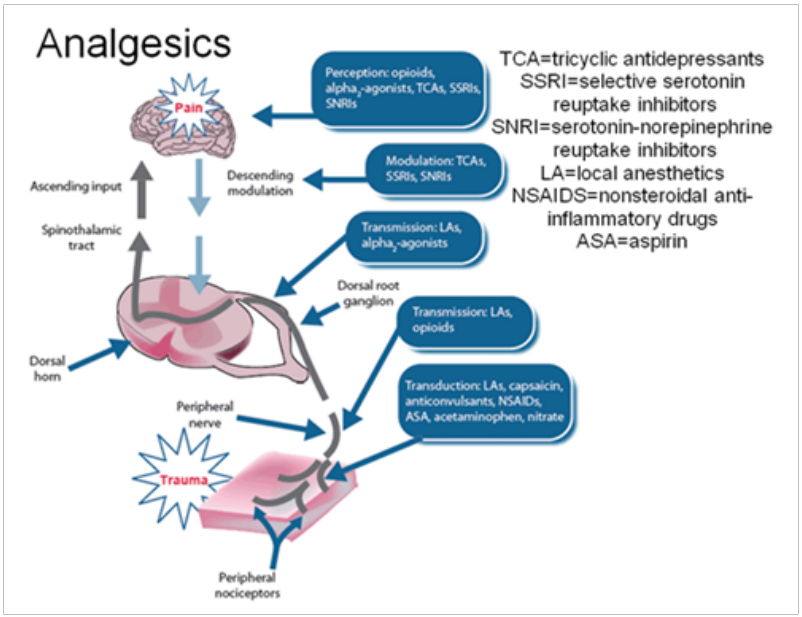

Figure 1 Site of analgesic action on the pain pathway.

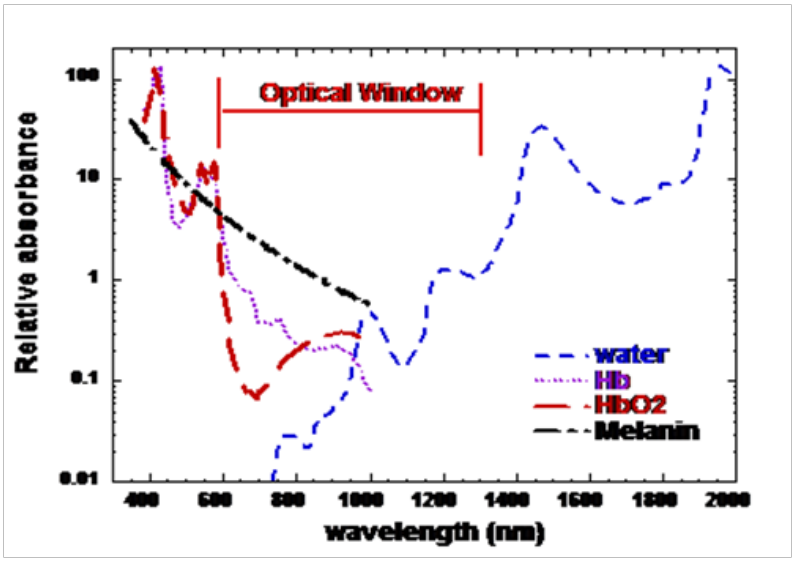

Figure 2 Tissue optical window.

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Mechanisms of LLLT (Figure 3)

For low-power visible or near-infrared light to have an effect on a biologic system, the photon must be absorbed by electronic absorption bands belonging to a photon acceptor or chromophore (first law of photobiology).[16] A chromophore is a molecule (or portion of a molecule) which imparts a color to a compound (e.g. chlorophyll, hemoglobin, myoglobin, cytochrome c oxidase, other cytochromes, flavin, flavoproteins or porphyrins).[17] The "optical window" in a tissue describes a range of wavelengths where the penetration of light into tissue is maximized by employing red and near-infrared wavelengths.[18] The optimum wavelength has been estimated to be around 810 nm. Mitochondria are "the cellular power plants" in our cells and as such they convert food molecules and oxygen into energy (ATP) by oxidative phosphorylation. It has been proposed that cytochrome c oxidase (COX) is the primary photo-acceptor for the red-NIR wavelength range in mammalian cells.[19] Nitric oxide (NO) produced in mitochondria can inhibit respiration by binding to COX and displace oxygen especially in injured or hypoxic cells.[20] It is proposed that LLLT can photo-dissociate NO from COX and reverse the mitochondrial inhibition of respiration due to excessive NO binding.[21] The process of light mediated vasodilation was first described by RF Furchgott[22] in 1968, and his research on the biological properties of nitric oxide eventually led to the award of a Nobel Prize in 1998.[23] LLLT is able to produce a shift in the overall cell redox potential in the direction of greater oxidation by increasing reactive oxygen species (ROS) and decreasing reactive nitrogen species (RNS).[24–30] The long-term effects of LLLT are thought to be due to the activation of various transcription factors by the immediate chemical signaling molecules produce from mitochondrial stimulation by LLLT. The most important of these signaling molecules are thought to be ATP, cyclic-AMP, NO and ROS.[16]

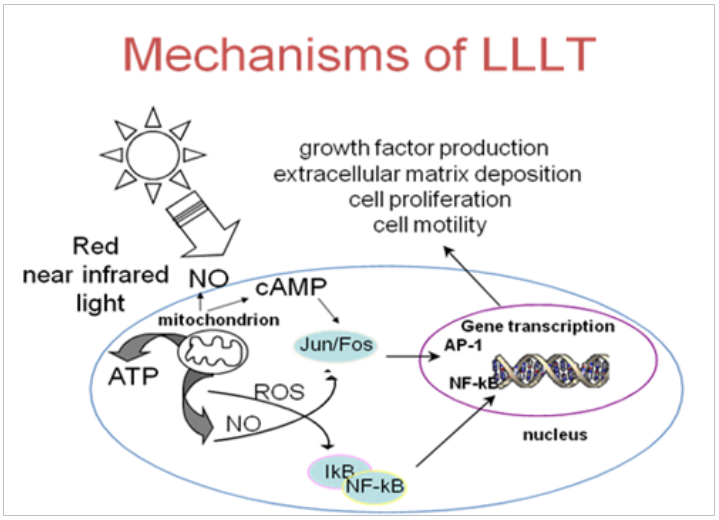

Figure 3 Mechanisms of LLLT.

LLLT at low doses has been shown to enhance cell proliferation of fibroblasts,[31–34] keratinocytes,[35] endothelial cells[36] and lymphocytes.[37,38] The mechanism of proliferation is thought to result from photo-stimulation of the mitochondria leading to activation of signaling pathways and up regulation of transcription factors eventually giving rise to increases in growth factors.[31,39–42] LLLT can enhance neovascularization, promote angiogenesis and increase collagen synthesis to aid in the healing of acute[43] and chronic wounds.[44–46] It has been observed in many studies, that LLLT exhibits a biphasic dose response curve,[47,48] where by lower doses of light are more effective than much higher doses. These low doses of light have demonstrated the ability to heal skin, nerves, tendons, cartilage and bones. This biphasic dose response curve may have important implications for LLLT for pain relief for the following reasons. Low-intensity LLLT stimulates mitochondria and raises mitochondrial membrane potential[49–51] and might be supposed to be more likely to increase metabolism and transport of action potentials in neurons rather than decrease it. However, much higher intensity LLLT produced by a focused laser spot acting on a nerve has the opposite effect, inhibiting mitochondrial metabolism in c-fibers and a-delta fibers and reducing mitochondrial membrane potential, thereby inducing a nerve blockade (see below).

LLLT in the treatment of pain

Acute orthopedic conditions such as sprains,[52,53] strains, post-surgical pain, a whiplash injury,[54] muscular back pain, cervical or lumbar radiculopathy,[55,56] tendinitis[57,58] and chronic conditions such as osteoarthritis,[59–64] rheumatoid arthritis, frozen shoulder,[65] neck and back pain,[56] epicondylitis,[66] carpal tunnel syndrome[67,68] tendinopathy,[69] fibromyalgia [70], plantar fasciitis [70], post tibial fracture surgery[9] and chronic regional pain syndrome are amenable to LLLT. Dental conditions producing pain such as orthodontic procedures,[71] dentine hypersensitivity,[72] and third molar surgery[73] respond well to treatment with LLLT. Neuropathic pain conditions can also be treated such as post herpetic neuralgia,[74] trigeminal neuralgia10, and diabetic neuropathy.[75] Due to the wide spectrum of conditions one would surmise that multiple mechanisms can operate to achieve pain relief.

The peripheral nerve endings of nociceptors, consisting of the thinly myelinated A∂ and unmyelinated, slow-conducting C fibers, lie within the epidermis. This complex network transduces noxious stimuli into action potentials. Moreover these nerve endings are very superficial in nature and thus are easily within the penetration depths of the wavelengths used in LLLT (Figure 4). The cell bodies of neurons lie within the dorsal nerve root ganglion, but the elongated cytoplasm (axons) of the neurons extends from the cell body to the bare nerve endings in the surface of the skin. The direct effect of LLLT are initially at the level of the epidermal neural network, but the effects move to nerves in subcutaneous tissues, sympathetic ganglia, and the neuromuscular junctions within muscles and nerve trunks.

LLLT applied with a sufficient level of intensity causes an inhibition of action potentials where there is an approximately 30%

neural blockade within 10 to 20 minutes of application, and which is reversed within about 24 hours.[76] The laser application to a peripheral nerve does have a cascade effect whereby there is suppressed synaptic activity in second order neurons so that cortical areas of the pain matrix would not be activated. Adenosine triphosphate (ATP) is the source of energy for all cells, and in neurons this ATP is synthesized by mitochondria while they are located in the dorsal root ganglion. These mitochondria are then transported along the cytoskeleton of the nerve by a monorail system of molecular motors. LLLT acts like an anesthetic agent, in that both LLLT and anesthetics have been shown to temporally disrupt the cytoskeleton for a matter of hours as evidenced by formation of reversible varicosities or beading along the axons, which in turn cause mitochondria to "pile up" where the cytoskeleton is disrupted.[77] The exact mechanism for this effect is unknown but it is not a thermal action. It has been shown that LLLT at the correct dose decreases mitochondrial membrane potential (MMP) in DRG neurons and that ATP production is then reduced[78] so perhaps the lack of ATP could be cause of this neural blockade. The most immediate effect of nociceptor blockade is pain relief which occurs in a few minutes and has been shown by the timed onset of a conduction blockade in somatosensory-evoked potentials (SSEPs).[76] This inhibition of peripheral sensitization not only lowers the activation threshold of nerves but also decreases the release of pro inflammatory neuropeptides (i.e. substance P and CGRP). In persistent pain disorders this reduction of tonic input to activated nociceptors and their synaptic connections, leads to a long-term down-regulation of second-order neurons.[78] The modulation of neurotransmitters is a further possible mechanism of pain relief, as serotonin and endorphin levels have been shown to increase in animal models[79,80] and following laser treatment of myofascial pain in patients.[81] Thus LLLT can have short, medium and long term effects. Fast acting pain relief occurs within minutes of application, which is a result of a neural blockade of the peripheral and sympathetic nerves and the release of neuromuscular contractions leading to in a reduction of muscle spasms.[82,83]

In the medium term there is a decrease of local edema and a reduction of inflammation within hours to days.[84] The action of LLLT in reducing swelling and inflammation has been well established in animal models as well as in clinical trials. The numbers of inflammatory cells has been shown to be reduced in joints injected with protease,[85] in collagen-induced rheumatoid arthritis,[86] and in acute pulmonary inflammation.[87] The expression levels of pro-inflammatory cytokines have been shown to be reduced by LLLT in burn wounds,[88] in muscle cryo lesions[89] and in delayed type hypersensitivity.[90] The long term effects of LLLT occur within a week or two and can last for months and sometimes years as a result of improved tissue healing.

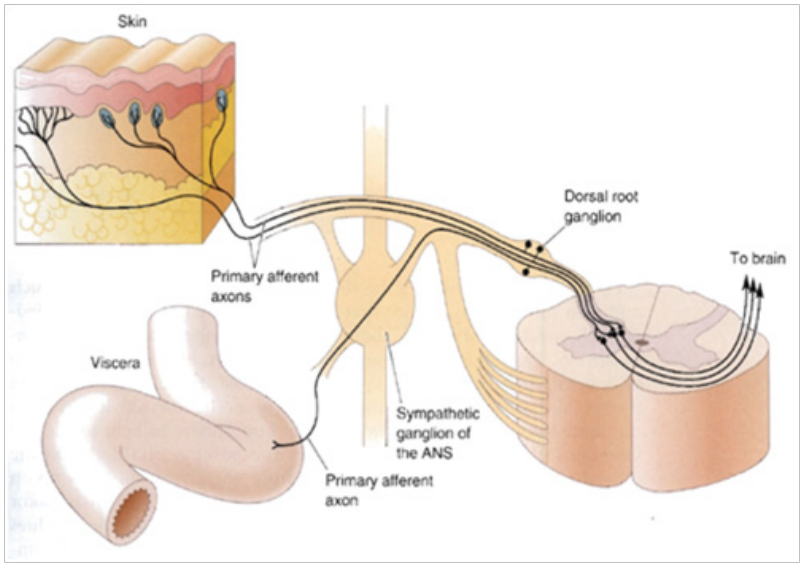

Figure 4 Mechanisms of LLLT.

LLLT parameters

For LLLT to be effective, the irradiation parameters (wavelength, power, power density, pulse parameters, energy density, total energy and time) need to be within certain ranges. The best penetrating wavelengths in the range of 760-850nm and may achieve a light density of 5mW/cm^2 at 5cm deep when the beam power is 1Watt and surface density is 5W/cm^2. There are four clinical targets for LLLT:

1. The site of injury to promote healing, remodeling and reduce inflammation.
2. Lymph nodes to reduce edema and inflammation.
3. Nerves to induce analgesia.
4. Trigger points to reduce tenderness and relax contracted muscle fibers.

Treatment times per point are in the range of 30 seconds to 1 minute. As little as one point may be treated in simple cases, but as many as 10 to 15 points may be treated for more complex dysfunction such as cervical or lumbar radiculopathy.

The potential hazards are mostly ocular, as some LLLT devices are lasers, though increasingly LLLT devices have become LEDs. In most cases, LLLT devices emit divergent beams (not focused or collimated), so the ocular risk diminishes over distance. Manufacturers are obliged to provide the nominal ocular hazard distance (NOHD) within their user instructions. ANSI 2 136.3 (2011) is the current definitive USA document on laser safety in healthcare environments (www.ansi.org) and IEC60825 is the International Standard. Part 8 provides guidelines for the safe use of laser beams on humans (www.iec.ch).

The North American Association for Laser Therapy conference in 2010 held a consensus meeting on safety and contraindications. Their main recommendations were:

1. Eyes - Do not aim laser beams into the eyes and everyone present should wear appropriate safety spectacles.

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2. Cancer - Do not treat over the site of any known primary carcinoma or secondary metastasis unless the patient is undergoing chemotherapy when LLLT can be used to reduce side effects such as mucositis. LLLT however can be considered in terminally- ill cancer patients for palliative relief.
3. Pregnancy- Do not treat directly over the developing fetus.
4. Epileptics - Be aware that low frequency pulsed visible light (<30Hz) might trigger a seizure in photosensitive, epileptic patients.

The adverse effects of LLLT have been reported to be no different from those reported by patients exposed to placebo devices in trials.

Orthopedic outcomes

According to the more than 4000 studies on pub.med.gov, it can be concluded that the majority of laboratory and clinical studies have demonstrated that LLLT has a positive effect on acute and chronic musculoskeletal pain. Due to the heterogeneity of populations, interventions and comparison groups, this diversity means that every single study has not been positive. Pain is a very complex condition which presents in different forms with an interplay of mechanical, biochemical, psychological and socioeconomic factors. It is extremely challenging to compare LLLT to other treatments, and LLLT regimens are complicated by different lengths of treatment, all without standardization of wavelengths and dosages. Currently, there have been no long-term (greater than 2 year follow up) human clinical studies that have evaluated LLLT. The overall positive short term clinical studies in addition to strong laboratory studies should give the clinical confidence that LLLT may be beneficial for many individuals suffering from musculoskeletal pain, regardless of the cause. Consideration of evidence based treatment studies for LLLT has led to the determination that LLLT is classified as experimental/investigational by insurance companies (BCBSKS 2013), while the American Academy of Orthopedic Surgeons has no recommendations for or against its use. With FDA approval for temporary relief of muscle and joint pain, this underlines the need for further well-designed clinical studies.

Conclusion

One has to be realistic about the therapeutic use of LLLT. The previous discussion has shown that LLLT is beneficial for pain relief and can accelerate the body's ability to heal itself. LLLT has a long history and strong basic science evidence, which supports its use in pain management. It has few side effects and is well tolerated by the elderly. A laser or LED does not correct situations involving structural deficits or instabilities whether in bone or in soft tissue. Also, LLLT should only be used as an adjuvant therapy for pain relief in patients with neuropathic pain and neurologic deficits. Successful outcomes, like all medical management, depend on good clinical skills linked with an understanding of the nature of injury, inflammation, repair, pain, and the mechanism of laser and LED effects.

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