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SPECIAL ARTICLE
PAIN AND PHYSICAL MODALITIES

Low-intensity LASER and LED (photobiomodulation therapy) for pain control of the most common musculoskeletal conditions

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ABSTRACT

Pain is the most common reason for physician consultations and the number one reason for missed work or school days is musculoskeletal pain. Pain management is utilized for easing the suffering and improving the Quality of Life of those living with chronic pain. Over the past several decades, physicians have become increasingly willing to prescribe opioids to manage pain. However, the opioid use can cause side effects as poor coordination, sedation, mood swings, depression, and anxiety combined with a dependence on the drugs. In the rehabilitation setting, patients benefit most when their health providers utilize a multimodal approach combining different types of therapies and when patients take on a significant role in optimal management of their own pain. The use of light as a therapeutic alternative form of medicine to manage pain and inflammation has been proposed to fill this void. Photobiomodulation therapy applied in the form of low-intensity Light Amplification by Stimulated Emission of Radiation (LASER) and light-emitting diode (LED) has been shown to reduce inflammation and swelling, promote healing, and reduce pain for an array of musculoskeletal conditions. There is evidence that photobiomodulation therapy reduces pain intensity in non-specific knee pain, osteoarthritis, pain post-total hip arthroplasty, fibromyalgia, temporomandibular diseases, neck pain, and low back pain. Therefore, the purpose of this paper was to present the up-to-dated evidence about the effects of low-intensity LASER and LED (photobiomodulation therapy) on pain control of the most common musculoskeletal conditions. We observed that the photobiomodulation therapy offers a non-invasive, safe, drug-free, and side-effect-free method for pain relief of both acute and chronic musculoskeletal conditions as well as fibromyalgia.

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Pain

Pain is the most common reason for physician consultations in the USA[1] and the number one reason for missed work or school days is musculoskeletal pain. One out of three Americans is affected by chronic pain annually.[2] According to the Centers for Disease Control and Prevention, 50 million adults in the United States have chronic daily pain, with 19.6 million adults experiencing high impact chronic pain that interferes with daily life or work activities.[3] Patients with acute and chronic pain in the United States face a crisis because of significant challenges in obtaining adequate care, resulting in profound physical, emotional, and societal costs. The cost of pain

to the United States is estimated at between $560 billion and $635 billion annually.[4] Pain can be classified as acute, subacute, or chronic. Acute pain is characterized by short duration, less than or equal to 6 weeks. Subacute pain is characterized by 7 to 12 weeks (3 months) of duration. While chronic pain is characterized by more than three months of duration.[5] Pain caused by a tissue damage normally resolves in a period of a few days to three months. However, acute pain can progress into chronic pain when it persists beyond the healing process and expected timeframe for tissue injury resolution due a maladaptive mechanism.[6] Pain management is utilized for easing the suffering and improving the Quality of Life of those living with chronic pain.

Pain management

Opioids are commonly used for acute and chronic pain.[7, 8] Over the past several decades, physicians have become increasingly willing to prescribe opioids to manage pain. However, at the same time, in the United States this escalating use of prescribed opioids has been accompanied by a sharp increase in opioid related mortality.[9] Meanwhile, in Europe, the prescription of opioids was four times lower than in the Unites States in 2015.[10] The opioid crisis describes both the medical overuse and subsequent addiction by patients to opioid prescription and synthetic drugs. Opioid side effects include poor coordination, sedation, mood swings, depression, and anxiety combined with a dependence on the drugs.[11] The damage to an individual can affect all facets of day-to-day life with the increased risk of fatal overdose. All management of pain using opioids carry a risk of misuse. Therefore, the benefits and harms should be carefully evaluated when prescribing opioids. Moreover, opioids should be used with the lowest effective dose for the shortest period possible.[12] Despite the side effects of opioids, they are often used as a healthcare modality as they are effective as analgesics. However, in the wake of the opioid crisis, research efforts have turned towards several non-pharmacological solutions to management of pain. There is a growing need to implement novel pain control modalities to reproduce the highly effective activity of opioids without their side effects. In the rehabilitation setting, patients benefit most when their health providers utilize a multimodal approach combining different types of therapies and when patients take on a significant role in optimal management of their own pain. While pain care has grown more sophisticated, the most effective care still is not widely available. The use of light as a therapeutic alternative form of medicine to manage pain and inflammation has been proposed to fill this void. Among of the options there is photobiomodulation therapy (PBMT) which is a non-thermal and non-ionizing light therapy applied in the form of Light Amplification by Stimulated Emission of Radiation (LASER), most specifically low-intensity laser, and red and/or near infrared low-intensity light-emitting diodes (LEDs).[13]

LASER and LED (photobiomodulation therapy)

PBMT found to have profound biological effects on tissue including increased cell proliferation,[14] accelerating the healing process, promoting tissue regeneration, preventing cell death,[15] anti-inflammatory activity[16] and relief of pain.[17] Therapeutic exposure to low intensity of red and/or near infrared light is commonly referred to as "low intensity" because of its use of light at energy densities that are low compared to other forms of laser therapy that are used for ablation, cutting, and thermally coagulating tissue.[18] Heat is a compounding limitation in achieving optimal phototherapeutic effects. As surface heating of the skin increases, the biological effect begins to decrease. Photothermal damage occurs when light energy deposition occurs faster than thermal diffusion, and the temperature of the target tissue rises.[19] The photobiological-photochemical phenomena promoted by PBMT are like photosynthesis carried out by plants. To enable the visible light of low intensity to affect any living biological system, the energy-carrying photons must be absorbed by electrons belonging to a photoreceptor or chromophore of the target biological system.[20] One of the basic mechanisms of PBMT is the stimulation of mitochondria,[21] which are thought to be a key target in the phototherapeutic mechanism of action acceleration of electron transfer by photons in the visible and near infrared region of the light spectrum[22] via the modulation of cytochrome c-oxidase (CCO) activity. This stimulation leads to increased adenosine triphosphate (ATP) production, modulation redox, and induction of transcription factors.[23]

PBMT on pain control

Pain results when a stimulus causes action potentials to rapidly propagate along a nerve cell. These action potentials are primarily due to an expulsion of positively charged sodium ions (Na+) and an influx of potassium (K+) ions into the nerve cell altering the electrical potential across the membrane. PBMT is directly absorbed by

receptors within the bi-lipid cellular membrane of nerve cells. The peak absorption of lipids is in the 905 nm to 910 nm range.[24] Once absorbed, the PBMT light will increase the porosity of the cellular membrane, allowing for a reabsorption of sodium ions and expulsion of potassium ions across the cellular membrane to rebalance the sodium-potassium pump and remove the pain signal at source. This will prevent the nerve from reaching threshold like how opioids cause postsynaptic inhibition.[25] The direct effect of PBMT is initially at the peripheral nerve endings of nociceptors, consisting of the thinly myelinated A delta (A∂) and unmyelinated, slow-conducting C fibers, within the epidermis.[2] When PBMT is applied to peripheral nerves, de-polymerization of the microtubules in Aδ and C-fibers occur from redox modulation resulting from the acceleration of the electron transport chain.[26] ATP and mitochondrial membrane potential (MMP) is decreased, limiting Na+, K+, and ATPase which maintains normal electrophysiological balance of the nerve. This works to block proinflammatory mediators such as prostaglandin E_2 (PGE_2), interleukin (IL)-6, and tumor necrosis factor alpha (TNF- α), in addition to blocks acetylcholine to eliminate muscle spasms. The result is a decrease in stimulation of nociceptors in the periphery and a decrease in the pain being transmitted by C-fibers and Aδ fibers. PBMT applied with a sufficient dose of energy has an inhibitory effect on nerve action potentials that create analgesia in as little as 10 to 20 minutes following treatment.[27] For chronic pain, the treatment must be done every 24 hours, as the microtubules regenerate and pain will return. PBMT can be indicated to temporary relief of minor muscle and joint pain, arthritis, and muscle spasm, relieving stiffness, promoting relaxation of muscle tissue, to temporarily increase local blood circulation where heat is indicated, symptomatic relief and management of chronic and intractable pain, adjunctive treatment for postsurgical, and post-trauma acute pain. There is evidence that PBMT has positive effects on decrease pain intensity in musculoskeletal conditions such as non-specific knee pain,[28] osteoarthritis,[29, 30] fibromyalgia,[31-33] temporomandibular disorders,[34-36] neck, shoulder and back pain,[17, 37, 38] and also in management of pain after total hip replacements.[39] The use of PBMT in the abovementioned musculoskeletal conditions have a direct impact on decreased use of pharmacologic agents, including non-steroidal anti-inflammatory drugs (NSAIDs) and opioids. The combination of good evidence and virtually no side effects make PBMT ideally suited to become an alternative for all future pain treatments. To date, no adverse effects have been demonstrated with the use of PBMT. However, some contraindications for its use should be highlighted: areas of active carcinoma, areas of infection, and thoracoabdominal and pelvic region in pregnant women. In this study we present the up-to-dated evidence about the effects of PBMT, *i.e.*, low-intensity laser therapy and red and/or infrared low-intensity light-emitting diode therapy, on pain control of the most common musculoskeletal conditions. Evidence on the effects of high-intensity lasers have been excluded as this therapy is not currently considered PBMT as it promotes thermal effects.

Non-specific knee pain

Among the musculoskeletal conditions, there is evidence that PBMT is effective in treating non-specific knee pain.[28] A randomized controlled trial (RCT) recruited 86 patients from five clinical sites (three chiropractic, one physical therapy, and one combination practice) and evaluated the effects of PBMT as an adjunct modality to standard care (*i.e.*, physical therapy or chiropractic therapy) on non-specific knee pain. The PBMT protocol consisted of 12 treatments in addition to standard rehabilitation exercises, given 3 times a week for four weeks. It was used a multi-wavelength PBMT (1 super-pulsed laser, 4 red LEDs and 4 infrared LEDs). Energy was directed to the knee (250 Hz × 1 minute at 5 locations around the patella) as well at lumbar spine (1000 Hz × 2 minutes to the affected side), inguinal lymphatics (1000 Hz × 2 min) and popliteal artery (50 Hz × 3 min). The results demonstrated a decreasing trend in reported Visual Analog Scale (VAS) pain scores at treatments 10 and 12 and resulted in a 50% improvement (15% greater than the placebo group). This outcome was maintained in the follow-up phase when repeated VAS reporting was collected 30 days following the conclusion of the therapy. In addition, a significant increase in physical functioning was demonstrated and was maintained through the 30 days follow-up visit. Therefore, the results suggested that although standard care is effective in treating knee pain, the addition of PBMT enhances clinical outcomes such as intensity of pain and physical functioning.

Osteoarthritis

It has been observed that PBMT, when used alone or in association with exercise programs, has positive effects on osteoarthritis reducing intensity of pain.[29, 30] A recent systematic review,[30] focused in evaluate the association of PBMT and exercises to treat knee osteoarthritis, included 7 RCTs (N.=339). Although in some included RCTs,[40, 41] PBMT was able to decrease the intensity of pain, there was a controversy regarding the effects of PBMT in associa-

tion with exercise programs. The heterogeneity related to PBMT parameters, frequency of sessions, and exercise protocols did not allow to conduct a meta-analysis in this study. Some recent RCTs using PBMT with 904 nm wavelength (frequency of 9500 Hz, energy of 0.78 J per site, 8 irradiation sites)[42] and 808 nm wavelength (continuous output, energy of 4 J per site, 7 irradiation sites each side of knee)[43] showed that PBMT associated with an exercise program was not superior to placebo in decrease intensity of pain in knee osteoarthritis. However, a letter to the editor pointed out that the dose applied by De Paula Gomes *et al*.[42] it was not adequate to achieve positive effects.[44] In contrast, other systematic review with meta-analysis[29] included 22 RCTs (N.=1089) evaluating the effects of PBMT, used alone or in association with exercise, on knee osteoarthritis. Overall, the results demonstrated that intensity of pain was reduced by PBMT when compared with placebo at the end of treatment sessions and during follow ups at 1 to 12 weeks later. In addition, the subgroups analysis demonstrated that pain was reduced when recommended doses of PBMT was applied, *i.e.*, the irradiation on the knee joint line/synovia was ≥4 J using 780-860 nm wavelength PBMT and/or ≥1 J using 904 nm wavelength.[45, 46] The mean duration of the whole treatment was 3.53 weeks in the recommended PBMT doses, while 3.7 weeks in the non-recommended PBMT doses.

Total hip arthroplasty

Osteoarthritis degrades the articular cartilage and damages the subchondral bone.[47] In advanced stages of osteoarthritis, abnormal remodeling of cartilage and formation of osteophytes irreversibly destroy the affected joint. When conservative treatments fail or fail to manage pain, hip osteoarthritis results in the need for a total hip arthroplasty. Total hip arthroplasty is known for being an extreme surgical procedure and despite the improvement in postsurgical Quality of Life (QoL), the management of postoperative pain is inadequate.[48] There is a rapid accumulation of inflammation following total hip arthroplasty. There is a high prevalence of persistent postoperative pain after total hip replacement.[49] In this case, PBMT can be an alternative tool to treat these patients. A RCT[39] evaluated the effects of PBMT (5000 Hz, 5 minutes, 40 J at 5 sites directly over the surgical incision) on pain and inflammation in 18 postsurgical hip arthroplasty patients. It was observed that the active PBMT group experienced significantly ($P<0.05$) decreased pain that was 82% greater than placebo immediately following surgery. This demonstrates the effectiveness of PBMT as an alternative to analgesic medication and offers a viable means of managing pain postoperatively. Additionally, modulation of the inflammatory process following the arthroplasty postoperatively was observed in the group treated with PBMT-sMF which possibly contributed to decreased pain.

Fibromyalgia

Another musculoskeletal condition where PBMT can be used is for fibromyalgia. A RCT investigated the effects of PBMT after each session of a functional exercise program to treat fibromyalgia. Twenty-two patients were treated with exercise plus placebo or exercise plus PBMT (808 nm wavelength, continuous output, energy of 4 J per point, 8 points at quadriceps, 6 points at hamstrings, and 3 points at gastrocnemius). The results showed that there was no difference between exercise plus placebo and exercise plus PBMT in decrease intensity of pain in patients with fibromyalgia.[50] In contrast, there is evidence of positive results in treating patients with fibromyalgia with PBMT, including a decrease in pain between 6-8 points, number of tender points (from 14 to zero), and Fibromyalgia Impact Questionnaire (FIQ) scores, besides to an increase in function.[32] Additionally, a larger clinical trial[33] evaluated PBMT and exercise for managing pain and improving the Quality of Life of 160 women suffering from fibromyalgia. The study evaluated the application of PBMT in 11 tender points for 300 s. A multi-wavelength PBMT was used: 1 super-pulsed laser with 905 nm wavelength and frequency of 1000 Hz, 4 red LEDs with 640 nm wavelength and frequency of 2 Hz, and 4 infrared LEDs with 875 nm wavelength and frequency of 16 Hz. The energy irradiated per site was 39.3 J per site. Patients were allocated into 2 different sessions: acute (1 session) and chronic (10 weeks, 2 times weekly), each with 4 groups: placebo-control, PBMT, exercise, and PBMT + exercise. The results demonstrated a large effect for both PBMT and exercise groups (nearly 50% greater than placebo), however the PBMT and the PBMT + exercise groups experienced the greatest reduction in pain when compared to control and exercise alone. When looking at the reduction in the number of tender points, it should be noted that the PBMT + exercise group significantly reduced the overall number of tender points. It is important to highlight that exercise is the recommended protocol to treat fibromyalgia. The original European League Against Rheumatism evaluated 34 clinical trials with a minimum of 2495 participants.[51] It was observed 47 different exercise interventions, including aerobic, that assisted with improvement in pain. In addition, resistance training also demonstrated

significant improvement in pain and function. The conclusion of this study was that nearly all exercise was equally effective, and no evidence suggest a superiority of one over the other. Therefore, the evidence for inclusion of exercise to treat fibromyalgia was strong (100% agreement). In addition, PBMT has been shown to improve exercise performance.[52] Therefore, the finding of a synergistic effect between the interventions is not surprising. Therefore, although there are some negative results using PBMT to treat fibromyalgia,[50] a systematic review and meta-analysis suggested that PBMT is a noninvasive, well-tolerated treatment for fibromyalgia to relieve discomfort and decrease pain.[31]

Temporomandibular disorders

Temporomandibular disorders are musculoskeletal and neuromuscular conditions of the temporomandibular joint complex and surrounding muscles responsible for causing pain or dysfunction, earache, headache, and facial pain. Most patients improve the condition with a combination of noninvasive therapies, including pharmacotherapy and physical therapy treatment. Among the physical therapy, PBMT has been used to treat pain due temporomandibular disorders.[36] A pilot RCT compared the effects of PBMT against placebo on intensity of pain in adolescents and young adults with temporomandibular disorder. PBMT was irradiated with 780 nm wavelength, energy of 1 J per site at 4 sites on the masseter muscle and anterior temporal muscle on each side of the face. It was observed that PBMT was not superior to placebo in decrease intensity of pain in the temporomandibular disorder patients.[53] In contrast, another RCT evaluated the immediate and short-term effects of different energies (2.62 J, 5.24 J and 7.86 J) of PBMT on 60 women with temporomandibular disorders.[34] Treatment was only performed extra-orally and administered to the anterior, middle, and posterior temporal muscle (three points) as well as the upper and lower masseter muscles (two points) bilaterally, totaling 10 points on each volunteer, with a radiance area of 4 cm^2 per point. A multi-wavelength PBMT was used: 1 super-pulsed laser with 905 nm wavelength and frequency of 1000 Hz, 4 red LEDs with 640 nm wavelength and frequency of 2 Hz, and 4 infrared LEDs with 875 nm wavelength and frequency of 16 Hz was used. It was observed that pain intensity decreased significantly, with a median decrease of 2.2 - 2.7 pain points on a 10-point scale, when patients were treated with PBMT. The median decrease in pain was maintained for 48 h post treatment. Additionally, a RCT further evaluated the intraoral effects of bilateral PBMT of the lateral pterygoid muscle on temporomandibular disorders.[35] Two groups of 15 women were allocated into active or placebo PBMT. A multi-wavelength PBMT also was used. However, it was delivered an energy of 39.27 J per site (four sites of irradiation). Six sessions held 3 times a week, for 2 weeks, of 300 seconds or 40 J was applied to each lateral pterygoid muscle. Analyzing the outcomes, PBMT was found to be significantly more effective than placebo for pain ($P \leq 0.01$) and functioning ($P \leq 0.04$). However, the best effect was observed following the 6th visit. The first above-mentioned study may have demonstrated better outcomes from applying the PBMT to more muscles involved in temporomandibular disorders (anterior, middle, and posterior temporal muscle (three points) as well as the upper and lower masseter muscles (two points) while the second study only treated the lateral pterygoid. Finally, a recently systematic review and network meta-analysis[36] included 16 RCTs and concluded that PBMT applied with energy density not more than 10 J/cm^2 was able to decrease intensity of pain after the end of treatment in patients with temporomandibular disorders when compared to placebo. This positive effect was maintained in the follow-up phase a month after the end of treatment. In contrast, when doses ranging from 10 J/cm^2 to 50 J/cm^2 and from 50 J/cm^2 to 100 J/cm^2 the effects on pain intensity were worse than placebo. Overall, the favorable outcomes in pain reduction support the inclusion of PBMT in the multimodal approach to treat temporomandibular diseases. Future treatments should continue to focus on less invasive modalities such as PBMT and consider including both protocols for the optimization of outcomes regarding pain reduction. As demonstrated, there is an effect with both intra- and extra-oral applications.

Neck pain

In the rehabilitation setting, PBMT also can be used in the management of neck pain. Non-specific neck pain is one of the most common types of chronic pain, and nearly 67% of world's population will experience chronic non-specific neck pain at least once in their lives.[54] It was demonstrated that PBMT with an 830 nm wavelength, frequency of 1000Hz, energy of 7 J per site, applied in 6 sites was not superior to placebo in decrease intensity of pain in patients with cervical myofascial pain syndrome.[55] However, there is strong evidence that PBMT reduces pain in patients with neck pain. A systematic review and meta-analysis[17] published in the renowned *The Lancet* included 16 RCTs (N.=820) and assessed the efficacy of PBMT on neck pain. The authors concluded that pain is reduced immediately

after treatment in acute neck pain and up to 22 weeks after the end of treatment in chronic neck pain. In addition, this systematic review observed that there is a distinct dose-response pattern for each wavelength of PBMT. Therefore, a therapeutic window was established. For PBMT with 820-830 nm, it was established a mean dose per point ranged from 0.8 to 9.0 J, with irradiation times of 15-180s. For PBMT with 904 nm, it was established a mean dose per point ranged from 0.8-4.2 J, with irradiation times of 100-600 s.

Low back pain

Additionally, low back pain is also a common health condition worldwide that possible might be treated with PBMT. There is evidence that PBMT modulate PGE_2 levels in patients with chronic non-specific low back pain, indicating a possible mechanism involved in analgesic effects.[56] A systematic review and meta-analysis[57] included 12 RCTs (N.=1046) and observed that although PBMT decreased pain in some particular studies,[37, 38] in general PBMT was not able to decrease pain in patients with low back pain. However, the conclusion of this systematic review was that the quality of evidence was low, *i.e.*, future research is likely to change the estimated effect and will have a significant impact on confidence in the effect. Therefore, further studies are necessary to investigate the effects of PBMT on low back pain, in addition to the optimization of PBMT parameters and dosage to patients with low back pain.[57, 58]

PBMT parameters

Despite all positive effects with PBMT on painful conditions, it is important to keep in mind that the PBMT parameters used are crucial for the success of the therapy. A sufficient cover area should be irradiated, and a sufficient irradiation time should be applied. In addition, optimal dosing is a key to trigger positive effects with PBMT.[59] PBMT has a biphasic response pattern, *i.e.*, PBMT can be either stimulatory (repair) or inhibitory (pain relief) depending on the delivered dose.[59] Therefore, the selection of doses should be based on a therapeutic window to each health condition whenever available, to achieve better results with PBMT.[17, 29, 45, 46]

Conclusions

In conclusion, low-intensity LASER and LED (PBMT) offers a non-invasive, safe, drug-free, and side-effect-free method for pain relief of both acute and chronic musculoskeletal conditions as well as fibromyalgia. Although there are other effective light-based therapies, these were not focused in this study. In our paper, we observed that, although there are several clinical studies demonstrating the analgesic effect of PBMT, some health conditions such as knee pain and postoperative pain after total hip replacement need to be further investigated due the limited research available. Some negative results were also found; however, these results are mostly due to the lack of previous optimization of the PBMT parameters used. Furthermore, we observed that most systematic reviews did not assess the overall quality of evidence, which is important to demonstrate confidence that the effect estimate is adequate to support this therapeutic approach.

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