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THE UTILITY OF PHOTOBIOMODULATION AS A SUPPLEMENT TO ORTHOBIOLOGIC INTERVENTIONS: A CURRENT CONCEPT REVIEW

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Abstract

Several mechanisms may influence recovery and act as a complementary intervention to regenerative medicine. One area of consideration that may improve clinical outcomes in patients receiving regenerative medicine treatments is the utilization of supplementary interventions referred to as regenerative rehabilitation. One such intervention may be the use of light therapy also known as photobiomodulation (PBM). Terms synonymous with PBM include low-level light therapy (LLLT), low-power laser irradiation or cold laser. As a musculoskeletal intervention, PBM is administered via a mechanism that creates light through optical amplification. These interventions describe a form of PBM or light therapy that uses specific parameters to target tissues through direct or indirect contact with or without heat or structural tissue alterations. PBM may improve treatment outcomes based on synergistic effects that are thought to modulate inflammation and facilitate cellular repair. This manuscript provides an overview of the current evidence supporting the use of PBM as a complementary intervention to regenerative medicine with a focus on managing conditions related to the musculoskeletal system.

Keywords: *Laser; light therapy; physical agent; regenerative rehabilitation*

INTRODUCTION

Novel regenerative medicine products (e.g., orthobiologics) have gained considerable attention in the musculoskeletal specialties, owing to the promise of decelerating the disease process and potentially offering a superior long-term solution to existing conservative treatments.[1] One area of interest that may improve clinical outcomes in patients receiving regenerative medicine treatments is the utilization of synergistic interventions often referred to as regenerative rehabilitation. The term regenerative rehabilitation is an umbrella term for numerous treatments, including but not limited to specific physical therapy or rehabilitation interventions (e.g., eccentric overloading and blood flow restriction training) and physical agents such as shockwave and photobiomodulation (PBM).

Terms synonymous with PBM include low-level light therapy (LLLT), low-power laser irradiation or "cold laser." These interventions describe a form of PBM (light amplification by stimulated emission of radiation) or light therapy that uses specific parameters to target tissues through direct or indirect contact without heat or structural tissue alterations.[2] For clarity, the term PBM will be used hereafter. PBM is more comprehensively defined as a form of light therapy that utilizes non-ionizing light sources, including lasers, light-emitting diode (LED), and broadband light in the visible and infrared spectrum.

PBM may improve treatment outcomes based on synergistic effects postulated to modulate inflammation and enhance cellular repair. This manuscript provides an overview of the current evidence supporting the use of PBM with a focus on implications to manage conditions related to the musculoskeletal system.[2]

As a musculoskeletal intervention, PBM is administered via a mechanism that creates light through optical amplification. Since PBM is a form of light therapy that uses various light sources, including laser, a brief overview of laser classification is presented. Specifically, there are "generally" four main classes of laser as defined by the international engineering consortium. The primary purpose of the different classifications is to evaluate potential danger, particularly related to possible eye damage or heat-related injury. Classes 1–3 are often referred to as cold laser as they do not generally generate heat.

Class 1 – Includes lasers that do not emit optical radiation greater than what would be considered exposure limits for the eye. (e.g., CD player or laser printer)

Class 2 – Includes low powered lasers (<1 mW) that may potentially cause harm to an individual's eye. (e.g., laser pointers) Class 2 lasers are used for the management of musculoskeletal conditions.

Class 3 – These lasers are medium powered in nature, and necessitate measures to avoid viewing directly into the laser beam. Although medium powered (up to 500mW), these lasers do not generate heat. Precautions include avoiding direct exposure to eyes or exposure via a reflected beam (e.g., spectrometry). Class 3 lasers are used for the management of musculoskeletal conditions.

Class 4 – These lasers are the highest class relative to danger and are greater than 500 mW. There are 2 types of class 4 lasers: thermal class 4 which create heat and can be used to burn through tissue during surgery, and the second type, a photochemical class 4 laser. A photochemical class 4 laser would be used to deliver laser therapy to target tissue and may be used to treat musculoskeletal tissue. Unintended exposure could lead to severe eye and skin damage (they create heat). Also, combustible materials should not be in the same vicinity as it may be a fire hazard.

As noted in the classification system, lasers are measured by their power but are also categorized by their energy. Power is measured in wattage; the higher the wattage, the higher the power. However, energy is measured in Joules. The energy of a laser is what is being delivered to the tissues. For example, a higher-power laser would deliver the same number of Joules as a lower-power laser in a short time. Or another way to interpret the interaction of power and energy would be that, in a similar time frame, a higher-powered laser could deliver considerably more energy to tissues than a lower-powered unit. Higher-powered lasers offer the ability to target large volumes of tissue as well due to energy efficiency.

A definitive consensus on the mechanisms by which PBM interacts with and influences tissue physiology does not exist.[3–5] A proposed theory claims light radiated by the PBM device is absorbed by or scattered throughout the tissues.[3–5] The interaction of light and tissue partly depends on the ability of light to penetrate into the tissues.[3,4] The wavelength of the light delivered during PBM usually falls within red and near-infrared wavelengths (600–700 nm and 780–1100 nm).[3,4] These wavelengths seem most appropriate for PBM, given there is more effective tissue penetration in these ranges because of reduced light scattering and reduced light absorption by hemoglobin and melanin.[3,4] It should be noted that evidence suggests light wavelengths in the 700–780nm spectrum have less

capacity to be absorbed and minimal biochemical activity and therefore are not suggested for PBM.[3,4] When determining the depth of tissue penetration, shorter wavelengths between 600 and 700 nm are used to treat superficial tissues and longer wavelengths between 780 and 950 nm are used to penetrate deeper tissues.[3]

The light interacting with tissue induces molecular and cellular changes that may increase mitochondrial activity and oxygen metabolism. The increased cellular activity subsequently alters reactive oxygen species (ROS) and produces vasodilative effects on the smooth muscle in blood vessels.[3–5] This process may result in improved modulation of adenosine triphosphate (ATP) production, immune system response, cellular transcription, oxygen consumption, and the synthesis of protein/collagen.[3–5]

The application of PBM typically occurs through direct or indirect, superficial, non-invasive contact with tendinous or other structures from PBM or an LED.[3,4,6,7] PBM utilizes red or near-infrared light with lower energy density to prevent any heating effect that may alter tissue properties.[3] Other application parameters include wavelength, frequency, power density, pulse structure, application points, and duration of application. These parameters can be modified based on the desired treatment effect. Ultimately, the goal of PBM in orthopedic medicine is to enhance tissue healing, reduce pain and inflammatory modulation.

Theoretically, the resultant increase of ATP production, immune system response, cellular transcription, oxygen consumption, and protein synthesis that may occur with PBM application supports the tissue healing process.[3–5] These effects may enhance healing through increased oxygen delivery to the tissues, which increases immune responses through modified mast cell activity.[3] PBM has also been recommended to manage inflammation and pain by reducing pro-inflammatory cellular markers/cytokines and increasing the production of peripheral endogenous opioids.[8] However, most mechanistic studies have been performed *in vitro*, which limits the extrapolation of these concepts to human subjects.

EVIDENCE FOR PHOTOBIOMODULATION

Evidence from a published systematic review with meta-analysis exploring the use of PBM for treating various musculoskeletal conditions in numerous body regions including but not limited to the shoulder, elbow, hand, knee, and foot exists and may be used to guide clinical decisions.[9] A significant limitation in the body of evidence for PBM is the non-uniformity of study design.[2,9] The PBM therapies investigated in these studies have a variety of applicators known as diodes, which may be infrared, super-pulsed, or a combination of these. Considerable variability exists in the specific PBM type and application method. Accordingly, the non-uniformity in PBM devices and parameters makes it difficult to compare studies.

Researchers have suggested that the large variability in PBM research methodology and lack of evidence for specific PBM parameters is a barrier to normalizing the use of PBM in the clinic setting.[2] Use of the World Association for Photobiomodulation Therapy (WALT) guidelines is recommended to standardize research, measure the effectiveness of PBM treatment, and aid clinicians in eliciting appropriate treatment effects.[29] Based on current best evidence, clinicians may find it necessary to individualize PBM therapy treatments until research trials begin to standardize reporting and usage of PBM parameters. Furthermore, declared power and beam diameter vary between manufacturers. As a result, greater standardization of equipment is an area of future development in this industry.[10]

PBM therapy can be used independently or as adjuvant therapy. PBM therapy, used with other interventions, such as exercise and electrical stimulation, aids in pain management and inflammatory modulation for conditions such as tendinopathy.[6,7,11–16] Yet, there is a paucity of evidence in human subjects on PBM therapy application as an adjuvant therapy to orthobiological regenerative medicine interventions such as platelet-rich plasma, bone marrow, and fat. Accordingly, this article aims to provide practical guidelines for the use and application of PBM therapy as an adjuvant intervention for orthobiologics.

Upper Extremity

Research has evaluated the use of PBM in treating shoulder and lateral epicondyle tendinopathy (LET).[7,16–18] The evidence for shoulder tendinopathy suggests photobiomodulation can reduce pain on a visual analog scale as an independent modality or alongside other interventions such as exercise.[17] A systematic review by Haslerud et al.[17] found that PBM reduced pain to a greater extent than heat, ice, ultrasound, placebo PBM, or no treatment when used for a 2–12 week period for patients with shoulder tendinopathy. This study also found that PBM therapy improved global health status when compared to placebo or no treatment.[17]

Numerous studies have investigated the use of PBM for LET.[7,16,18] Tonk et al.[18] compared the use of PBM and PRP therapies and found that PBM was superior in acute management of Nirschl pain scores (2 weeks), but PRP outperformed PBM in Nirschl pain scores at 3-month follow up.[18] The limitations in the study may be influenced by increased pain scores from baseline in the PRP group, which comparatively made the PBM therapy attain lower pain scores.[18] Nonetheless, PBM may help manage an exacerbation of pain or acute presentations.

Further investigation on the use of PBM to treat LET is conflicting. Bjordal et al.[7] conducted a meta-analysis on placebo-controlled trials focused on independent PBM or PBM combined with exercise to treat pain and global health status related to LET. Results showed that PBM therapy was superior to placebo when used independently or alongside exercise for short-term pain reduction and improvements in global health status (disability) in individuals with LET after treatment and at 3–8 week follow-ups.[7] This investigation also found that, of 13 trials evaluated, 7 used a 904-nm wavelength PBM with direct tendon irradiation. These parameters tended to show superior improvements in pain and global health status when compared to other parameters.[7]

In contrast to the research supporting PBM use for LET, an umbrella review conducted by Mamais et al. [16] which included the results from Bjordal et al.[7] suggested poor evidence to support the use of PBM for the treatment of LET. Mamais et al[16] reasoned that poor support for using LLLT to treat pain and overall improvement for treating LET was likely due to heterogeneous parameters, research design, and conflicting evidence. Nevertheless, the authors concluded that although the evidence is inconclusive for whether LLLT is effective in managing symptoms of LET, clinicians should not eliminate LLLT as an option for treating LET as additional studies investigating and testing optimal treatment dosages are warranted.

Lower Extremity

Photobiomodulation has been used to modify symptoms after total hip arthroplasty.[12] Evidence shows that PBM leads to similar levels of post-treatment pain but a greater reduction in inflammation when compared to placebo for patients after total hip arthroplasty.[12] In adults with knee osteoarthritis, PBM studies compared to placebo have shown superior reductions in pain when used independently or combined with interferential current (IFC).[14] Furthermore, PBM with IFC led to greater improvement in pain during walking than IFC or placebo.[14] Other studies investigating 40 to 80-year-old individuals with knee osteoarthritis showed that when comparing exercise, exercise and placebo PBM, or exercise and active PBM, all groups had similar outcomes in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) function scores.[13] However, this evidence also showed PBM and exercise led to greater improvements in numeric pain rating scores than the other conditions.[13]

PBM's use to treat patellofemoral pain syndrome yields conflicting evidence. Pocai et al.[19] showed that PBM treatment produced no meaningful changes in pain (except for pain associated with landing a jump), function, and self-reported outcome measures when used as an independent treatment and compared to a control group in young females. Gavish et al.[11] showed that treatment of anterior knee pain in soldiers and police officers with physical therapy and active PBM was superior in short-term (4 week) outcomes when compared to sham PBM and physical therapy. However, this study also revealed no significant difference in outcomes for

anterior knee pain at 3-month follow-up with participants in either group.[11]

For other lower extremity conditions, PBM therapy lacks clinical utility. Research indicates that PBM and rehabilitation were no better than rehabilitation alone to treat hamstring strain injury.[15] The use of active LLLT on adductor muscles of the thigh/groin in water polo players to alter inflammation, muscle damage, and performance measures showed no significant difference to placebo LLLT treatment.[20] However, research indicates that 4 weeks of photobiomodulation in a 12-week rehabilitation program with eccentric exercise outperformed placebo groups in reductions of the numeric pain rating scale and Achilles tendinopathy severity.[6]

PHOTOBIOMODULATION AS AN ADJUVANT THERAPY TO ORTHOBIOLOGICS

A clinical argument for combining the treatment effects of PBM and PRP could be made based on the potential synergistic effect of the two interventions. PBM and PRP, for example, could potentially be used concurrently to promote tissue and wound healing through increasing vasodilation (via PBM) and vasculogenesis/angiogenesis (via PRP) to reduce pain associated with tissue injury through increased peripheral endogenous opioid production.[3,8,21]

The current evidence for the use of PBM and PRP together has primarily come from theoretical animal models and cell studies.[22–24] Animal studies have shown that PRP combined with LED light may boost cell viability; however, wound closure in animals has been greatest when LED is used alone and less effective when combined with PRP. This may be due to decreased cell migration when PRP is administered alone or with LED.[23] Rat studies have shown that combining PBM and PRP to treat a lesioned gastrocnemius muscle had superior regeneration of cells, reduced area of injury, and greater blood vessel presence compared to PRP or PBM alone.[24]

In some individuals, and based on preparation, PRP may initially have a pro-inflammatory effect and increase pain acuity. Currently, it is unknown if the sequencing of PRP and PBM therapy is important for maximizing treatment effects. However, one may consider that using PBM after PRP may reduce or help manage an acute exacerbation initiated by PRP injection.[18] For example, either the injury site or the vials of prepared PRP or other orthobiologics may be subjected to PBM before being injected. In two studies that evaluated the effects of PRP combined with lipoaspirate and bone marrow aspirate (BMA) on knee osteoarthritis, the authors subjected the leukocyte-rich PRP and BMA to PBM before injection with positive outcomes in the cohort.[25,26] Although this is a feasible option for some, the effects of the PBM in the study are unknown given the case series nature and lack of control group of the studies.[25,26]

Further patient research is warranted to validate the safe and effective use of the combination of PRP and PBM. Should clinicians decide to combine the therapies, they would benefit from knowing which musculoskeletal conditions would respond favorably. Based on how PBM utilization in research and the intended treatment effects of PRP application, PBM and PRP could be combined when treating soft tissue injury, joint pathology, and joint inflammatory conditions including: knee osteoarthritis, knee pain related to soft issue injury or degeneration, and tendinopathies.[6,11–14,17,27]

CLINICAL RECOMMENDATIONS & APPLICATIONS FOR PHOTOBIOMODULATION THERAPY

Adequate Dosage and Parameters

The clinical suggestion is that PBM functions dose-dependently, which requires a certain range of parameters for treatment effectiveness.[28] The utility of specific LLLT parameters have been investigated for conditions such as shoulder tendinopathy and LET.[7,16,17] Accordingly, these investigations led authors to evaluate studies that explored adequate and inadequate PBM dosages compared to the parameters suggested by WALT. Studies have shown that adequate dose trials demonstrate superior pain reduction for shoulder tendinopathy, while inadequate dose trials have shown no

significant difference between PBM and controls over 2–12 week periods.[17] Other studies investigating PBM for treatment of LET have demonstrated that certain parameters, specifically a 904-nm wavelength PBM with a direct tendon application, led to superior improvement in pain and global health status compared to other PBM parameters.[7] Yet, a meta-analysis conducted by Clijsen et al. [9] revealed no difference in outcomes when comparing studies that did or did not follow WALT recommendations for dose and beam parameters and further concluded that outcomes were independent of the anatomical site treated.

Due to the conflicting evidence on effective parameters to use with PBM therapy, clinicians must decide whether using the WALT guidelines or direct evidence from empirical research trials is most appropriate for guiding the parameters of a PBM treatment. Therefore, it may be beneficial for clinicians to use PBM parameters based on specific research trials (Table 1). By using evidence from trials, clinicians may tailor PBM parameters for a particular condition, such as the time course of interventions and anatomical locations of PBM application (Table 2). Clinicians must recognize the evidence for treating specific conditions when choosing the most appropriate methods for selecting and applying PBM therapy.

PHOTOBIOMODULATION SAFETY CONSIDERATIONS

Any interventional modality, including PBM, used in clinical practice necessitates assessment of any precautions and contraindications. Evidential suggestions for major safety concerns or adverse reactions are seemingly lacking for using PBM.[3] However, the paucity of adverse events related to PBM raises the question of whether there is a general absence of negative effects or a lack of reporting adverse reactions. Safety considerations may vary depending on the variables involved when delivering PBM such as the light source. Some researchers suggest no safety concerns when using LEDs to deliver PBM therapy.[3] It should be noted that researchers have suggested that near-infrared light can pose a danger and cause potential damage to the retina of the eye and therefore, it is likely efficacious for clinicians and patients to use protective eyewear during PBM therapy sessions.[3] Furthermore, a major factor to consider when enforcing patient safety is direct contact which many of the PBM research protocols utilize.[7,12,13,20] Therefore, general infection or contamination precautions and disinfecting procedures of PBM devices must be considered as with any other modality that contact the patient. Additionally, cautious and protective contact is required when applying direct contact over open wounds or areas at risk for infection. According to the North American Association for Laser Therapy safety concerns and contraindications included epilepsy, pregnancy, eyes, and cancer (Table 3.)

CONCLUSION

While there is limited evidence on the combined use of PRP and therapeutic PBM therapy, the theoretical rationale may support the combined use of these therapies. The shared benefits of PRP and PBM seem to be in their ability to individually treat soft tissue and joint pathology for conditions including knee osteoarthritis, knee pain, and tendinopathies.[6,11–14,17,27,29] Thus, clinicians should consider the appropriate sequencing and timing of these therapies when using them in a care plan. PBM and orthobiologics could potentially promote tissue and wound healing through increasing vasodilation and angiogenesis, which may reduce associated pain through increases in peripheral endogenous opioid production.[3,8,21] Yet if the therapies seem to be counterproductive when applied together, then it may be that PBM can be applied with the intention to reduce pain rather than inflammation to allow a more manageable and less symptomatic inflammatory phase for the patient or simply as a means of mitigating the acute effects of inflammation from the injury.[18] The suggestion that a dose-response relationship exists has support but still needs to be verified by further research.[7,9,16,17] Therefore, clinicians must use the best evidence from research trials (see Tables 1 and 2) and clinical judgment when using PBM therapy.

Table 1. PBM Parameters used in Published Studies

Parameters	Laser Combination	Wavelength (nm)	Frequency (Hz)	Dose per point (J)	Number of points	Application time per point (s)	Energy Density (J/cm²)	Total Energy (J)	Peak Power (W)	Optical Output (mW)	Average Optical Output (mW)	Spot Size Area (cm²)	Pulse Repetition Frequency (Hz)	Power Density (mW/cm²)	Pulse Duration (ns)	Average power (mW)	Beam cross-sectional area (cm²)
Pain and Inflammation for total hip arthroplasty (Langella et al.) *	9 diodes. 1 super pulsed diode laser. 4 red LEDs. 4 infrared LEDs. Super pulsed diode laser parameters are listed to the right.	905	3000	0.81	5	300	2.9	39.8	8.5	N/A	2.7	0.4	N/A	9.66	N/A	N/A	N/A
Inflammation, muscle damage and sports performance (Zagatto et al.)	Infrared laser	810	Continuous optical output	3	16 (8 per leg)	30	107.14	48	N/A	100	N/A	0.028	N/A	3.57	N/A	N/A	N/A
Knee osteoarthritis (Alqualo-Costa et al.)	Gallium Arsenide probe	904	N/A	3	9	75	N/A	27	70	N/A	N/A	N/A	9500	N/A	60	40	0.5
Knee osteoarthritis (de Paula Gomes et al.) *	9 diode cluster device. 1 super pulsed diode laser, 4 red LEDs, 4 infrared LEDs. Super pulsed diode laser parameters are listed to the right.	905	1000	7.85 (per quadrant)	3 (quadrants)	60 (quadrant)	0.12	23.55	8.5	N/A	N/A	0.44	N/A	2.25	N/A	N/A	N/A
Acute management of PFPS/ Anterior knee pain (Gavish et al.) *	660/850nm LED cluster with single point laser and laser cluster. Green LED cluster parameters over the knee are below.	660/850	2.5	3	4	60	3	12	N/A	N/A	N/A	N/A	N/A	50	N/A	N/A	N/A
Achilles tendinopathy (Tumlity et al.)	Lightforce EX unit (Litecure LLC, Newark, NJ, USA)	810/980	100	150 (to each part of tendon)	3 (medial, lateral and posterior sections)	30	6.66	450	10	N/A	N/A	3	N/A	N/A	N/A	5	N/A

**Studies that used cluster emitter or laser with multiple diodes and various settings per diode type. Diode/emitter types: super pulsed, LEDs, infrared, or other. PBM: photobiomodulation.*

Table 2. PBM Parameter Suggestions

Diagnosis	Wavelength (nm)	Dose per Point (J)	Number of Application Points**	Application Time per Point (s)
Upper extremity tendinopathies (Bjordal et al.)*	904	0.6–1.2	5–7	120–600
Post-hip arthroplasty pain and inflammation (Langella et al.)	904	0.81	3–5 based on size of area	30–60
Knee pain (Gavish et al.)	660/850	3	4	60
Knee Osteoarthritis (Alqualo-Costa et al. and de Paula Gomes et al.)	904–905	3 or 7.85	3 or 9	60–75
Achilles Tendinopathy (Tumlity et al.)	810/980	150	3	30

**Based on paper and additional supplementary tables from Bjordal et al.[7]*

***The total number of distinct application contact points in the treatment region. All laser applications were provided via direct contact (Table adapted from WALT recommendations for PBM)(WALT, 2022)[29]*

PBM: photobiomodulation.

Table 3. Safety Precautions and Contraindications

Concern	Explanation
Epilepsy	Pulsed visible light may trigger a seizure in those susceptible to light.
Eyes	The beam should never be directed into the eyes, and appropriate safety classes should always be worn.
Pregnancy	Directed laser should never be utilized over or adjacent to a developing fetus
Cancer	Avoid regions with identified primary carcinoma or secondary metastasis. Exceptions may include mitigating side effects from chemotherapy or palliative relief for terminally ill patients.

REFERENCES

1. Obana KK, Schallmo MS, Hong IS, et al. Current trends in orthobiologics: An 11-year review of the orthopaedic literature. Am J Sports Med. Sep 2022;50(11):3121–29. https://doi.org/10.1177/03635465211037343
2. Wickenheisser VA, Zywot EM, Rabjohns EM, Lee HH, Lawrence DS, Tarrant TK. Laser light therapy in inflammatory, musculoskeletal, and autoimmune disease. Curr Allergy Asthma Rep. Jul 2 2019;19(8):37. https://doi.org/10.1007/s11882-019-0869-z
3. Chung H, Dai T, Sharma SK, Huang YY, Carroll JD, Hamblin MR. The nuts and bolts of low-level laser (light) therapy. Ann Biomed Eng. Feb 2012;40(2):516–33. https://doi.org/10.1007/s10439-011-0454-7
4. de Freitas LF, Hamblin MR. Proposed mechanisms of photobiomodulation or low-level light therapy. IEEE J Sel Top Quantum Electron. May-Jun 2016;22(3). https://doi.org/10.1109/jstqe.2016.2561201
5. Gao X, Xing D. Molecular mechanisms of cell proliferation induced by low power laser irradiation. J Biomed Sci. Jan 12 2009;16(1):4. https://doi.org/10.1186/1423-0127-16-4
6. Tumilty S, Mani R, Baxter GD. Photobiomodulation and eccentric exercise for Achilles tendinopathy: a randomized controlled trial. Lasers Med Sci. Jan 2016;31(1):127–35. https://doi.org/10.1007/s10103-015-1840-4
7. Bjordal JM, Lopes-Martins RA, Joensen J, et al. A systematic review with procedural assessments and meta-analysis of low level laser therapy in lateral elbow tendinopathy (tennis elbow). BMC Musculoskelet Disord. May 29 2008;9:75. https://doi.org/10.1186/1471-2474-9-75
8. Hagiwara S, Iwasaka H, Hasegawa A, Noguchi T. Pre-Irradiation of blood by gallium aluminum arsenide (830 nm) low-level laser enhances peripheral endogenous opioid analgesia in rats. Anesth Analg. Sep 2008;107(3):1058–63. https://doi.org/10.1213/ane.0b013e31817ee43e

9. Clijsen R, Brunner A, Barbero M, Clarys P, Taeymans J. Effects of low-level laser therapy on pain in patients with musculoskeletal disorders: a systematic review and meta-analysis. Eur J Phys Rehabil Med. Aug 2017;53(4):603–10. https://doi.org/10.23736/s1973-9087.17.04432-x
10. Girasol CE, Braz GA, Bachmann L, Celli J, Guirro RRJ. Laser light sources for photobiomodulation: The role of power and beam characterization in treatment accuracy and reliability. PLoS One. 2022;17(3):e0266193. https://doi.org/10.1371/journal.pone.0266193
11. Gavish L, Spitzer E, Friedman I, et al. Photobiomodulation as an adjunctive treatment to physiotherapy for reduction of anterior knee pain in combat soldiers: A prospective, double-blind, randomized, pragmatic, sham-controlled trial. Lasers Surg Med. Dec 2021;53(10):1376–85. https://doi.org/10.1002/lsm.23442
12. Langella LG, Casalechi HL, Tomazoni SS, et al. Photobiomodulation therapy (PBMT) on acute pain and inflammation in patients who underwent total hip arthroplasty-a randomized, triple-blind, placebo-controlled clinical trial. Lasers Med Sci. Dec 2018;33(9):1933–40. https://doi.org/10.1007/s10103-018-2558-x
13. de Paula Gomes CAF, Leal-Junior ECP, Dibai-Filho AV, et al. Incorporation of photobiomodulation therapy into a therapeutic exercise program for knee osteoarthritis: A placebo-controlled, randomized, clinical trial. Lasers Surg Med. Oct 2018;50(8):819–828. https://doi.org/10.1002/lsm.22939
14. Alqualo-Costa R, Rampazo É P, Thome GR, Perracini MR, Liebano RE. Interferential current and photobiomodulation in knee osteoarthritis: A randomized, placebo-controlled, double-blind clinical trial. Clin Rehabil. Oct 2021;35(10):1413–1427. https://doi.org/10.1177/02692155211012004
15. Medeiros DM, Aimi M, Vaz MA, Baroni BM. Effects of low-level laser therapy on hamstring strain injury rehabilitation: A randomized controlled trial. Phys Ther Sport. Mar 2020;42:124–30. https://doi.org/10.1016/j.ptsp.2020.01.006
16. Mamais I, Papadopoulos K, Lamnisos D, Stasinopoulos D. Effectiveness of low level laser therapy (LLLT) in the treatment of lateral elbow tendinopathy (LET): an umbrella review. Laser Ther. Sep 30 2018;27(3):174–86. https://doi.org/10.5978/islsm.27_18-OR-16
17. Haslerud S, Magnussen LH, Joensen J, Lopes-Martins RA, Bjordal JM. The efficacy of low-level laser therapy for shoulder tendinopathy: a systematic review and meta-analysis of randomized controlled trials. Physiother Res Int. Jun 2015;20(2):108–25. https://doi.org/10.1002/pri.1606
18. Tonk G, Kumar A, Gupta A. Platelet rich plasma versus laser therapy in lateral epicondylitis of elbow. Indian J Orthop. Jul 2014;48(4):390–3. https://doi.org/10.4103/0019-5413.136260
19. Pocai BL, Provensi É, Serighelli F, et al. Effect of photobiomodulation in the patellofemoral pain syndrome; randomized clinical trial in young women. J Bodyw Mov Ther. Apr 2021;26:263–7. https://doi.org/10.1016/j.jbmt.2021.01.003
20. Zagatto AM, de Paula Ramos S, Nakamura FY, de Lira FS, Lopes-Martins R, de Paiva Carvalho RL. Effects of low-level laser therapy on performance, inflammatory markers, and muscle damage in young water polo athletes: a double-blind, randomized, placebo-controlled study. Lasers Med Sci. Apr 2016;31(3):511–21. https://doi.org/10.1007/s10103-016-1875-1
21. Dohan Ehrenfest DM, Rasmusson L, Albrektsson T. Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF). Trends Biotechnol. Mar 2009;27(3):158–67. https://doi.org/10.1016/j.tibtech.2008.11.009
22. Gonçalves AB, Bovo JL, Gomes BS, et al. Photobiomodulation (λ = 808 nm) and platelet-rich plasma (PRP) for the treatment of acute rheumatoid arthritis in wistar rats. J Lasers Med Sci. 2021;12:e60. https://doi.org/10.34172/jlms.2021.60
23. Alzyoud JAM, Al Najjar SA, Talat S, Abu-Irmaileh B, Bustanji Y, Al-Shudiefat AAS. Effect of light-emitting diodes, platelet-rich plasma, and their combination on the activity of sheep tenocytes. Lasers Med Sci. Jun 2019;34(4):759–66. https://doi.org/10.1007/s10103-018-2657-8
24. Ozaki GA, Camargo RC, Koike TE, et al. Analysis of photobiomodulation associated or not with platelet-rich plasma on repair of muscle tissue by Raman spectroscopy. Lasers Med Sci. Dec 2016;31(9):1891–98. https://doi.org/10.1007/s10103-016-2067-8
25. Kolber MJ, Purita J, Fabio Santos Duarte Lana J, Salamh PA, Hanney WJ. The effect of combined bone marrow aspirate, lipoaspirate, and platelet rich plasma injection on pain, function, and perceived change amongst individuals with severe knee osteoarthritis. Biologic Ortho J. 2021;3(1):e29–e39. https://doi.org/10.22374/boj.v3i1.25
26. Kolber MJ, Purita J, Hanney WJ. The effect of combined bone marrow aspirate, lipoaspirate, and platelet-rich plasm injections on pain, function,

and perceived change amongst individuals with glenohumeral osteoarthritis. Biologic Ortho J. 2022 Nov. 30 [cited 2023 Jan. 30];4(SP1):e83–e95. Available from: https://biologicortho.com/index.php/BiologicOrtho/article/view/49

27. Chen X, Jones IA, Park C, Vangsness CT, Jr. The efficacy of platelet-rich plasma on tendon and ligament healing: A systematic review and meta-analysis with bias assessment. Am J Sports Med. Jul 2018;46(8):2020–32. https://doi.org/10.1177/0363546517743746
28. Zhevago NA, Samoilova KA. Pro- and anti-inflammatory cytokine content in human peripheral blood after its transcutaneous (in vivo) and direct (in vitro) irradiation with polychromatic visible and infrared light. Photomed Laser Surg. Apr 2006;24(2):129–39. https://doi.org/10.1089/pho.2006.24.129
29. World Association for Photobiomodulation Therapy (WALT). Recommended anti-inflammatory dosage for photobiomodulation (PBM/ Low Level Laser Therapy). WALT; 2022. https://waltpbm.org/wp-content/uploads/2022/11/Dosage-recommendation-904nm-REVISED-OCTOBER-2022.pdf
30. McKay J, Frantzen K, Vercruyssen N, Hafsi K, Opitz T, Davis A, Murrell W. Rehabilitation following regenerative medicine treatment for knee osteoarthritis-current concept review. J Clin. Orthop. Trauma. 2019 Jan-Feb;10(1):59–66. https://doi.org/10.1016/j.jcot.2018.10.018