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ORIGINAL ARTICLE

Adjunctive use of combination of super-pulsed laser and light-emitting diodes phototherapy on nonspecific knee pain: double-blinded randomized placebo-controlled trial

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Abstract Phototherapy with low-level laser therapy (LLLT) and light-emitting diode therapy (LEDT) has arisen as an interesting alternative to drugs in treatments of musculoskeletal disorders. However, there is a lack of studies investigating the effects of combined use of different wavelengths from different light sources like lasers and light-emitting diodes (LEDs) in skeletal muscle disorders. With this perspective in mind, this study aimed to investigate the effects of phototherapy with combination of different light sources on nonspecific knee pain. It was performed a randomized, placebo-controlled, double-blinded clinical trial. Eighty-six patients rated 30 or greater on the pain visual analogue scale (VAS) were recruited and included in study. Patients of LLLT group received 12 treatments with active phototherapy (with 905 nm super-pulsed laser and 875 and 640 nm LEDs, Manufactured by Multi Radiance Medical, Solon, OH, USA) and conventional treatment (physical therapy or chiropractic care), and patients of placebo group were treated at same way but with placebo phototherapy device. Pain assessments (VAS) were performed at baseline, 4th, 7th, and 10th treatments, after the completion of treatments and at 1-month follow-up visit. Quality of life assessments (SF-36®) were performed at baseline, after the completion of treatments and at 1-month follow-up visit. Our results demonstrate that phototherapy significantly decreased pain ($p<0.05$) from 10th treatment to follow-up assessments and significantly improved ($p<0.05$) SF-36® physical component summary at posttreatments and follow-up assessments compared to placebo. We conclude that combination of super-pulsed laser, red and infrared LEDs is effective to decrease pain and improve quality of life in patients with knee pain.

Keywords Knee pain · Super-pulsed laser · Light-emitting diodes · Musculoskeletal disorders

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Introduction

Analgesic drugs and nonsteroidal anti-inflammatory drugs (NSAIDs) are widely prescribed and used to treat the pain associated with musculoskeletal disorders [1]. However, these drugs treat only the symptoms and not the disease cause [2, 3]. They have been linked to a vast array of side effects related to long-term use [4, 5].

Phototherapy with low-level laser therapy (LLLT) and light-emitting diode therapy (LEDT) has arisen as an interesting alternative to pharmacological pain management. Recently, a systematic review provided evidence that visible and infrared light irradiation cause neural impairment, in particular in small diameter Aδ and C fibers that conduct nociceptive stimuli, which leads to analgesic effects [6].

The light-tissue interaction leads to modulation of release of inflammatory markers including PGE_2, TNF-α, IL-1β, and plasminogen activator. Phototherapy also modulates several aspects of the inflammatory process including edema and hemorrhagic formation, necrosis, neutrophil cell influx, and the activity of macrophages, lymphocytes, and neutrophils. Phototherapy has been shown to inhibit the NF–Kappa signaling pathway and to modulate expression of inducible nitric oxide synthase (iNOS) [7]. These mechanisms can also lead to analgesic effects promoted by phototherapy.

Evidence continues to supports the use of LLLT for osteoarthritis [8] tendinopathies [9, 10], back pain [11, 12], neck pain [13, 14], and more recently, skeletal muscle fatigue [15–22]. Additionally, LLLT or LEDT has virtually no side effects.

Phototherapy effects have been demonstrated in both LLLT and LEDT. The use of multiple light sources could represent a therapeutic advantage by providing concurrent energy delivery to multiple depths of penetration determined by the selected wavelengths. Cleary, there is a lack of studies, mainly clinical trials investigating the combined use of different wavelengths and those from different light sources. Therefore, the aim of this study was to investigate the effects of phototherapy with combination of different light sources on nonspecific knee pain.

Materials and methods

Subjects

A total of 86 patients were recruited for a double-blinded randomized placebo-controlled trial from five clinical sites (three chiropractic, one physical therapy, and one combined) across the Midwest, USA. All patients complained of acute or chronic knee pain, rated 30 or greater on the pain visual analogue scale. Patients were excluded if unable to understand and sign an informed consent, had active infection, pregnant or planning a pregnancy during the study period, or injections to the knee (steroids or NSAIDs) over the past month. The study was approved by the RCRC Independent Review Board's ethics review committee.

CONSORT flowchart summarizing experimental procedures and subjects is shown in Fig. 1.

Randomization and blinding processes

Each research site had two research consoles (A and B) that were randomized to either active or placebo by the manufacturer and programed with a preset research protocol. Both active and placebo emitters radiated visible red light, and opaque glasses were worn by the subjects, which further assisted with the blinding process. The research monitor and sites were blinded to the designation.

Subject randomization was achieved by a simple drawing of lots (A or B). Once subject randomization was determined, the blinded clinician was notified which console system to use

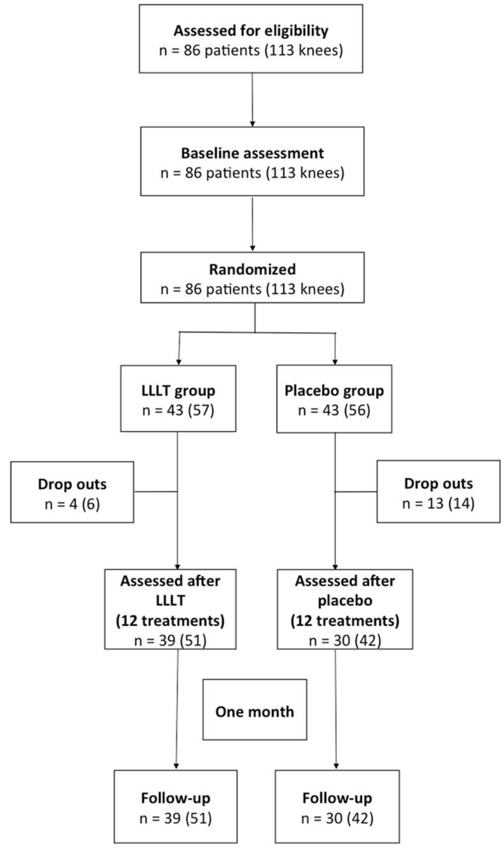


Fig. 1 CONSORT flowchart

and instructed not to discuss any treatment insights with the subjects.

Study design and protocol

The study consisted of 12 "treatment" visits and one follow-up visit 1-month posttreatment. The initial assessment determined if the inclusion/exclusion criteria were met, then randomization to either the LLLT or placebo groups occurred.

Procedures

The visual analogue scale (VAS) was used as a self-rating of their knee pain intensity. Subjects completed a VAS at six time points: baseline, prior to treatments 4, 7, 20, 12 (conclusion), and 30 days post follow-up. The SF-36® Health Survey was completed by subjects to measure their overall health pretreatment, end of treatments, and at follow-up. The survey includes eight domains: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. Scale scores for each of these eight health domains and two summary measures of physical and mental health, namely, the physical component summary and mental component summary were analyzed using the SF36 scoring software [23]. The higher the score, the less disability, i.e., a score zero is equivalent to maximum disability and a score of 100 is equivalent to no disability. A blinded assessor performed all assessments.

LLLT and placebo treatment protocols

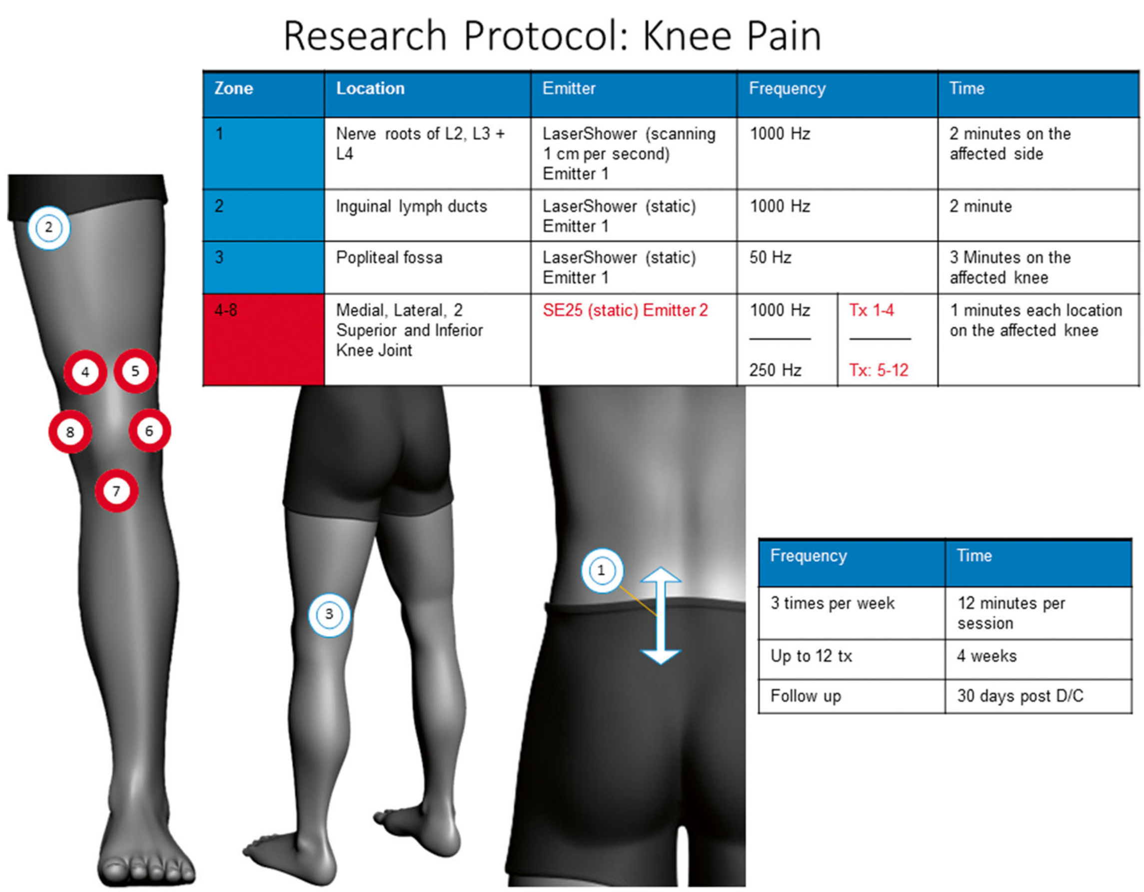
The protocol was divided into two phases (treatment and follow-up) each containing 4 weeks. Treatment phase began on the first day of treatment and included the recording of all baseline measurements. All subjects received 12 treatments over 4 weeks, three treatments per week, at least 2 days but no more than 3 days apart. Patients with pain in both knees were treated bilaterally.

LLLT and placebo applications were performed with the Multi Radiance Medical™ (Solon, OH, USA) MR4™ Super Pulsed Laser Console system using the LaserShower and SE25 emitters. Treatment protocol was 13 min per knee and includes both local and systemic targets on the affected side with the LaserShower emitter. Sites included scanning of the L2-4 nerve root for 2 min with 1,000 Hz, static overpressure of the inguinal canal lymph nodes with the same setting, and direct contact of the popliteal fossa at 50 Hz for 3 min, additionally, 1 min at 1,000 Hz to five sites around the knee (medial, lateral, two superior and inferior knee joint) with the SE25 emitter. After treatment 5, the setting on the SE25 changed to 250 Hz; however, the locations were the same. This phototherapy treatment protocol was performed based in feasibility study we have performed previously to start this clinical trial, Fig. 2 illustrates the active treatment or sham protocol. Phototherapy parameters were checked and provided by light-source manufacturer, Table 1 summarizes phototherapy parameters employed in this study.

At the conclusion of the treatment phase, patients entered the follow-up phase where baseline measures were taken and repeated 30 days after the last treatment.

Statistical analysis

The intention-to-treat analysis was followed. The primary outcome is pain measured by VAS scale at different time-points. Secondary outcomes are aspects assessed trough SF-36. The researcher that performed statistical analysis was blinded to randomization and allocation of volunteers in experimental groups.



Zone	Location	Emitter	Frequency		Time
1	Nerve roots of L2, L3 + L4	LaserShower (scanning 1 cm per second) Emitter 1	1000 Hz		2 minutes on the affected side
2	Inguinal lymph ducts	LaserShower (static) Emitter 1	1000 Hz		2 minute
3	Popliteal fossa	LaserShower (static) Emitter 1	50 Hz		3 Minutes on the affected knee
4-8	Medial, Lateral, 2 Superior and Inferior Knee Joint	SE25 (static) Emitter 2	1000 Hz 250 Hz	Tx 1-4 Tx: 5-12	1 minutes each location on the affected knee

Frequency	Time
3 times per week	12 minutes per session
Up to 12 tx	4 weeks
Follow up	30 days post D/C

Fig. 2 Treatment protocol employed in study

Table 1 Phototherapy parameters

MR4 Base Control Unit	SF25		LaserShower	
				
Number of super-pulsed lasers	1 super-pulsed laser		4 super-pulsed lasers	
Wavelength (nm)	905		905	
Frequency (Hz)	1000	250	1000	50
Peak power (W) - each	25		12.5	
Average optical output (mW) - each	2.5	0.625	1.25	0.0625
Power density (mW/cm2) - each	5.68	1.42	2.84	0.142
Dose (J) - each	0.15	0.0375	0.15	0.01125
Spot size (cm2) - each	0.44		0.44	
Number of red LEDs	4 red		4 red	
Wavelength (nm)	640		640	
Frequency (Hz)	2		2	
Average optical output (mW) - each	15		15	
Power density (mW/cm2) - each	16.66		16.66	
Dose (J) - each	0.9		1.8	2.7
Spot size (cm2) - each	0.9		0.9	
Number of infrared LEDs	4 infrared		4 infrared	
Wavelength of LEDs (nm)	875		875	
Frequency (Hz)	16		16	
Average optical output (mW) - each	17.5		17.5	
Power density (mW/cm2) - each	19.44		19.44	
Dose (J) - each	1.05		2.1	3.15
Spot size (cm2) - each	0.9		0.9	
Magnetic Field (mT)	35		35	
Aperture of device (cm2)	4		20	
Treatment Time (s)	60		120	180
Total energy delivered (J) separated via treatment number	Treatment 1-4	95.55	Site #1: LS 1000 Hz 120s = 16.2 J Site #2: LS 1000 Hz 120s = 16.2 J Site #3: LS 50 Hz 180s = 23.4 J Site #4-8: SF 1000 Hz 60s x 5 = 39.75 J	
	Treatment 5-12	95	Site #1: LS 1000 Hz 120s = 16.2 J Site #2: LS 1000 Hz 120s = 16.2 J Site #3: LS 50 Hz 180s = 23.4 J Site #4-8: SF 250 Hz 60s x 5 = 39.2 J	

Data were expressed as mean and standard deviation and were firstly tested regarding normal distribution using Shapiro–Wilk test. ANOVA test with repeated measurements for the time factor was performed to test between-groups differences (followed by Bonferroni post hoc test). The significance level was set at $p<0.05$.

Results

Eighty-six subjects assessed at baseline and randomly allocated in two different groups (LLLT group=43 and placebo group=43) were eligible to take part in study. None was excluded and 69 patients completed both phases. Table 2 summarizes demographic characteristics of participants that completed treatments in both groups.

No significant difference in pain at baseline between groups (LLLT group 56.14 SD±16.97, placebo group 63.57 SD±15.94; $p>0.05$). Pain decreased at the fourth and seventh treatment; however, no significant differences were observed between groups as well (fourth treatment LLLT group 39.84 SD±22.55, placebo group 43.19 SD±22.01 $p>0.05$; seventh treatment LLLT group 34.33 SD±21.92, placebo group 45.07 SD±24.48 $p>0.05$). In the 10th treatment, a significant decrease in pain ($p<0.05$) was observed in LLLT group (30.06 SD±20.62) compared to placebo group (46.05 SD±22.01). A significant decrease in pain ($p<0.05$) was also observed in LLLT group compared to placebo group in posttreatments (LLLT group 27.67 SD±22.86; placebo group 41.05 SD±24.08) and follow-up assessments (LLLT group 28.33 SD±20.06; placebo group 40.43 SD±22.24). Results regarding pain assessments are summarized in Fig. 3.

Figure 4 summarizes results regarding physical functioning, role physical, body pain, general health, and physical component summary assessed using SF-36. Results regarding mental health, social functioning, role emotional, vitality, and mental component summary are shown in Fig. 5.

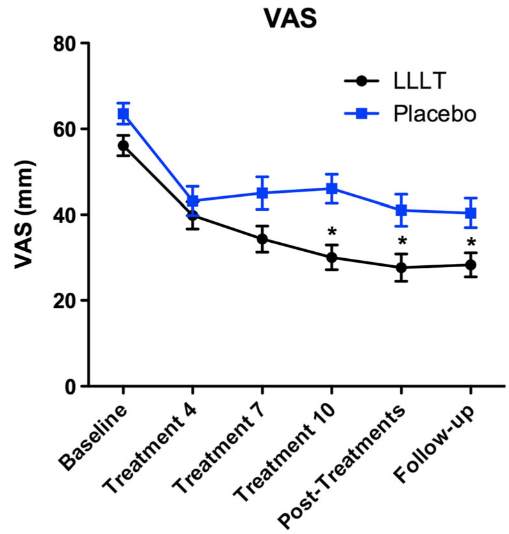


Fig. 3 Pain assessment using VAS score. *Values* are mean and *error bars* are standard error of the mean (SEM). $*p<0.05$ indicates statistically significant difference between LLLT and placebo groups

Discussion

Phototherapy research has shown both red and infrared wavelengths as well as the use of laser and LEDs have been effective for treating a variety of clinical conditions [24–27]. Presently, only a few studies have evaluated the effects of concurrent use of multiple wavelengths delivered by both lasers and LEDs [28].

Friedman et al. [29] found that combining multiple pulsing wavelengths improved electron transfer, enhancing ATP and neutralizing the ROS that accelerated the replacement of damaged cells. Since knee pain can have multiple etiologies occurring concurrently, resulting in a wide array of clinical findings and symptoms, this study sought to investigate if a combination of simultaneously delivered super-pulsed infrared laser and pulsed visible red and infrared light-emitting (diode) LED energy would be effective in reducing nonspecific knee pain.

Prior to initiating the study, clinical feasibility data were collected from three clinical sites. In order to treat a wide array of knee pain, their suggested feedback of including both local targets and systemic targets were incorporated into the study protocol. This segmental approach was considered since in clinical practice, it is common to have multiple symptoms present in knee pathologies in patients from various populations and clinical practice settings.

Dosage was determined upon recommendations by the World Association of Laser Therapy (WALT) [30] and clinical practice guidelines. According to Bjordal et al. [31], for acute pain, there is "strong evidence from 19 out of 22 controlled laboratory studies that low level laser therapy (LLLT) can modulate inflammatory pain by reducing level of biochemical parkers, neutrophil cell influx, oxidative stress and formation of edema and hemorrhage in a dose-dependent manner (median dose 7.5 J/cm2, range 0.3-19 J/cm2)." Initially, a slightly higher dose was delivered both locally and systemically to inhibit pain via photobioinhibition. de Almeida et al. [32, 33] noted a single dose can have varying effects on the tissue when the energy rate delivery is varied. Therefore, beginning with treatment 5 until the conclusion, the local dose was decreased by 1 J per site to stimulate tissue repair. This small variation in the rate of the energy delivery appears to have an impact (beginning with treatment 4) on the VAS score.

The treatment protocol began with the most proximal targets at the spine providing stimulation of cutaneous spinal

Table 2 Demographic data

LLLT group				Placebo group		
	Male	Female	Total	Male	Female	Total
Number	15	24	39	6	24	30
Mean age	54.00	58.42		51.83	57.96	

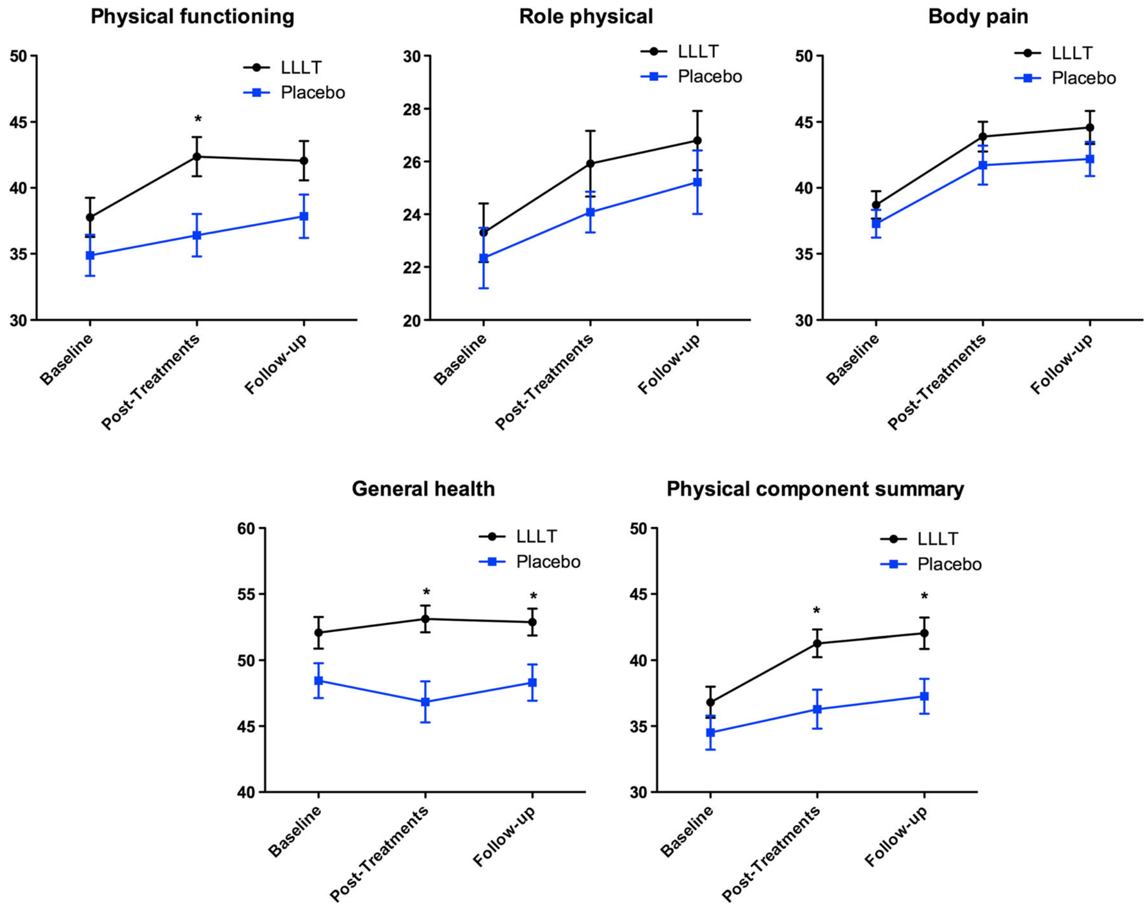


Fig. 4 Physical aspects (physical functioning, role physical, body pain, general health, and physical component summary) assessed using SF-36. *Values* are mean and *error bars* are standard error of the mean (SEM). *$p<0.05$ indicates statistically significant difference between LLLT and placebo groups

nerves [34] and where altering excitation and nerve conduction in peripheral nerves is possible [35]. Treatment proceeded to the groin to encourage lymphatic drainage and reducing potential edema and remove metabolites from the inflammatory processes [36, 37]. Stimulation of the posterior knee improves localized oxygen concentrations [38], improvement of microcirculation [39], and improved nitric oxide upregulation [40], and then anterior knee where LLLT modulates inflammatory processes [7]. By stimulating multiple treatment targets, it is suggested that clinical outcomes may be further enhanced. Approximately 40 % of the total energy was delivered directly to the knee while the remaining 60 % was divided between three other selected systemic "targets" including edema, circulation, and pain since these are common clinical symptoms seen across various nonspecific chronic pain [41].

While patients were randomized into either an active or placebo group, both groups also received standard care associated with their specific knee pain. Patients received either chiropractic or physical therapy treatments in addition to the phototherapy.

The results demonstrated a decreasing trend in reported visual analog scale (VAS) pain scores in the active treatment group after treatment 7. This reached statistical significance at treatments 10 and 12. This outcome was maintained in the follow-up phase when repeated VAS reporting was collected. The placebo group also improved, and there was a clinically significant drop in VAS pain reported of 35 %; however, statistical significance was not reached. It has been suggested that a 33 % decrease in pain represents a reasonable standard for determining that a change in pain is meaningful from the patient's perspective [42]. The active group resulted in a 50 % improvement (15 % greater than the placebo group) or one standard deviation improvement over the placebo group.

VAS is one of the most commonly used measures of pain intensity in research and clinical practice; however, it does not address the patient's perception of improvement, functional status, or quality of life. The multi-purpose SF-36 was used as a secondary measure to yield a profile of functional health and well-being scores as well as psychometrically based physical and mental health summary. The analyses of the SF-36 data demonstrated an increasing trend in physical component score

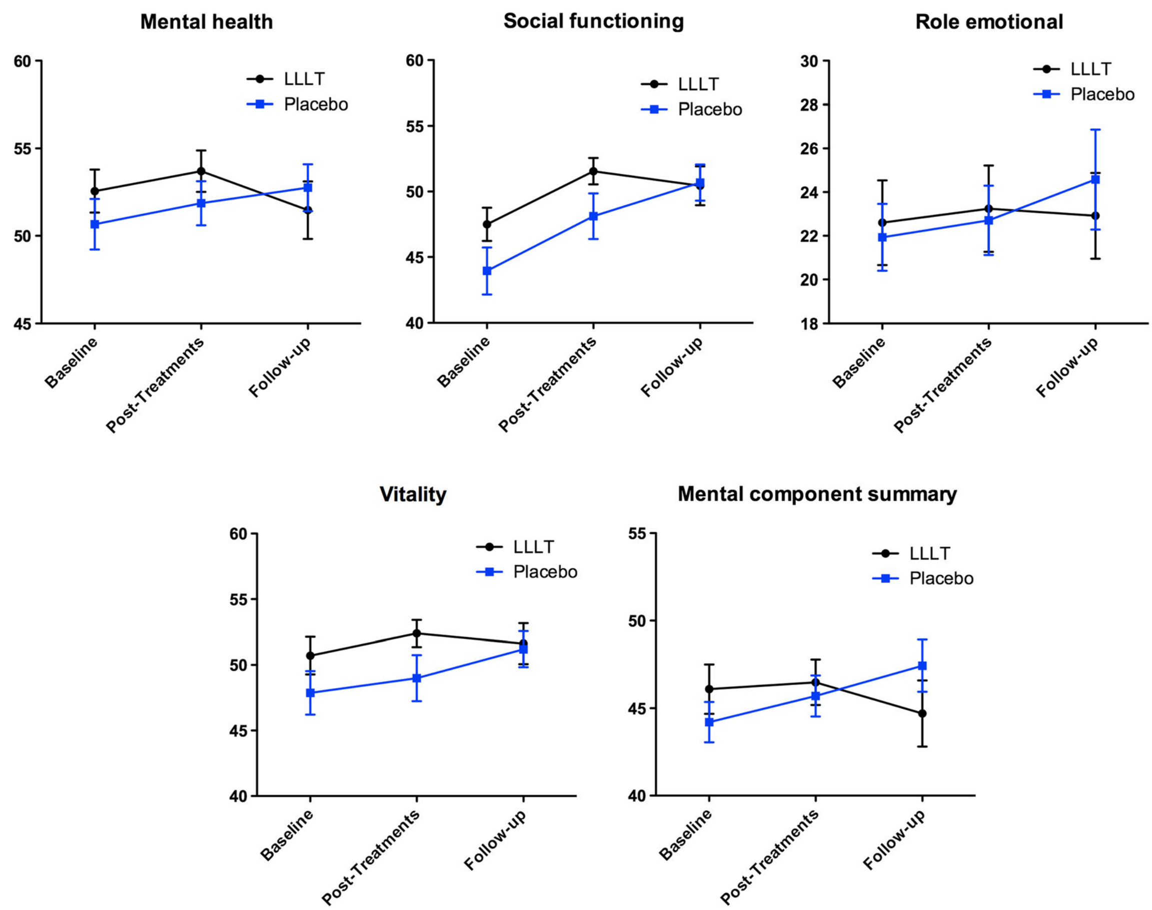


Fig. 5 Mental aspects (mental health, social functioning, role emotional, vitality, and mental component summary) assessed using SF-36. *Values* are mean and *error bars* are standard error of the mean (SEM)

(PCS), which also demonstrated a statistically significant improvement in physical functioning at the conclusion of both treatment and follow-up phases. The mental components score (MSC) did not show a significant improvement from pretreatment to 1-month follow-up.

Reported analgesic effects after only one treatment have been noted in the literature [43]. Within the study population, we found no clinical difference between groups until week 2, with significant differences being achieved after 10 visits. This is consistent with clinical practice and when treating older more chronic conditions. It is suggested that for more chronic conditions, more treatments provided for longer durations (lower energy delivery over longer time) done consistently might be necessary to significantly reduce pain. The sustained results at 1-month follow-up suggest that a minimum number is needed for longer-term pain control and improved function to be maintained. This may mean educating and encouraging patients to complete their entire course of treatment and not discharge themselves too quickly.

These results demonstrate that treatments outcomes for knee pain can be improved when phototherapy is added as an adjunctive modality. The combination of super-pulsed laser and visible red and infrared LED therapy can significantly improve pain ratings and enhance physical functioning of those who experience knee pain. The lack of improvement in SF-36 MCS, while both statistical and clinical significant results were demonstrated in VAS and PCS, does raise other clinical questions on the management of both acute and chronic pain. A limitation of the study is the inclusion of both acute and chronic knee pain. While this represents typical clinical practice, future studies could focus on the differentiation between acute and chronic knee pain to evaluate if the outcomes are more pronounced in one group more than the other.

Finally, the present study and others [44, 45] suggest that although other therapies (i.e., physical therapy or chiropractic therapy) are effective in treating knee pain, the addition of phototherapy enhances clinical outcomes.

Conclusion

Our findings lead us to conclude that combination of super-pulsed laser (905 nm) and light-emitting diodes with red (640 nm) and infrared (875 nm) wavelengths is effective to decrease pain and improve physical component in patients with nonspecific knee pain. Furthermore, the combination of different wavelengths and light sources seems to be an interesting therapeutic alternative in phototherapy field.

Competing interests Professor Ernesto Cesar Pinto Leal-Junior receives research support from Multi Radiance Medical (Solon, OH, USA), a laser device manufacturer. Douglas Scott Johnson is an employee and shareholder of Multi Radiance Medical (Solon, OH, USA). Anita Saltmarche and Dr. Timothy Demchak are educational consultants for Multi Radiance Medical (Solon, OH, USA).

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