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“Efficacy of low-level laser therapy for osteoarthritis of the knee”

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Abstract

Introduction: Osteoarthritis (OA) is a disease associated with numerous effects on quality of life (QoL) and activities of daily living (ADLs). In recent years, low-level laser therapy (LLLT) has been evaluated as a symptom management option for KOA due to its non-invasive mechanistic properties. The purpose of this paper is to assess the efficacy of LLLT as a modality of treatment to help reduce mild to moderate symptoms associated with KOA.

Methods: A search via PubMed database was made using the keywords "LLLT" AND "osteoarthritis" AND "knee" with additional specifiers resulting in 10 articles for review. Four articles were chosen to include due to their study parameters aligning with the purpose of this review. The remaining six articles were excluded.

Results: Of the four articles included, two were RCTs, one was a meta-analysis, and one was a systematic review. Each article looked at varying wavelengths and protocols for LLLT. The main outcomes of each of the four studies included function, pain control, and the effects on QoL.

Discussion: Results of the data show supportive evidence favoring the use of LLLT as a treatment method for symptomatic relief and pain management for individuals diagnosed with mild to moderate KOA. LLLT used in combination with exercise therapy (ET) has shown significant improvement on functional performance, QoL, and pain management. Therefore, laser therapy is suggested to be integrated into rehabilitation programs to improve muscle strength and functional performance. Further investigation is needed to determine the long-term benefits and the efficacy of treatment method for patients diagnosed with severe KOA.

Efficacy of low-level laser therapy for osteoarthritis of the knee

INTRODUCTION

Osteoarthritis (OA) of the knee is a heterogeneous disease associated with numerous effects on quality of life and daily functions. OA is the most common joint disease, affecting more than 240 million individuals worldwide, 32 million or more in the US alone.[1] Disease progression is characterized by damage and loss of articular cartilage, remodeling of subarticular bone, formation of osteophytes, weakening of periarticular muscles surrounding the knee joint, and ligament laxity.[2] Knee osteoarthritis (KOA), known to be the most common, tends to cause a significant burden to those affected. It is characterized by pathologic changes including synovitis, cartilage degeneration, subchondral bone remodeling, and osteophyte formation.[2] These changes can cause an array of symptoms include joint pain, stiffness, muscle weakness, limited range of motion, and functional limitations.[1,2] Risk factors for the development of KOA include increasing age, female sex, obesity, genetics, or major joint injury. Currently, it is among the most common causes of activity limitations in the adult population.[1]

Various modalities of therapy are recommended for symptom management including non-pharmacological, pharmacological, and surgical interventions. Treatment of KOA primarily consists of symptomatic relief completed by non-steroid anti-inflammatory drugs (NSAIDs), intra-articular injections, physical therapy, and exercise therapy due to disease-modifying treatment options not being available.[2] The main goals of treating KOA are to control symptoms, restore joint function, and prevent disease progression.[2] In recent years, low-level laser therapy (LLLT) has been evaluated as a symptom management option for KOA due to its non-invasive mechanistic properties. It has been shown to have significant clinical effects on pain relief through anti-inflammatory effects and analgesic properties.[2] The mechanism of action of LLLT

is photochemical, or photobiomodulation, which uses light to induce biochemical changes within the cells.[2] This releases neurotransmitters that are associated with pain modulation and anti-inflammatory mediators.[3] With this effect, LLLT has shown a reduction in inflammation within the synovial membrane of the knee, suppressing pain and inflammation; thus, stimulating healing, repair, and improvement in blood circulation.[3,4]

Currently, numerous research studies are being conducted to determine the most effective modalities of treatment for individuals diagnosed with KOA. Due to the high prevalence of this disease within the US population, it is crucial to explore additional therapeutic options available for symptom relief. The purpose of this paper is to evaluate the effect that LLLT has on symptom reduction, pain management, and improvement of quality of life alone or in conjunction with additional treatment modalities currently available.

METHODS

A search via PubMed database using the keywords “LLLT” AND “osteoarthritis” resulted initially with 83 articles. MeSH terms and Boolean operators were added to produce a final search of “LLLT” AND “osteoarthritis” AND “knee”. This resulted in 55 articles. Additional search filters were applied for RCTs, systematic reviews, and meta-analyses only. The date of publication was restricted to the last 5 years. Restrictions regarding English language and free full text available were the final specifiers added. This yielded 10 results. One of the articles used LLLT in combination with hyaluronic acid (HA) injections for symptom management for individuals with KOA. Due to LLLT being used in conjunction with HA injections, rather than alone for symptom relief, it was excluded from the study. Two articles were excluded from the study due to being a letter to the editor and/or not fitting within the search parameters. An additional article was excluded from the study due to only examining the

effects of high-intensity laser therapy for pain management, rather than LLLT. Lastly, two additional articles were excluded from the study due to being nonspecific for osteoarthritis of the knee. Ten studies were reviewed and four were selected. The selected studies analyzed were two randomized controlled trials (RCTs), one meta-analysis of RCTs, and one systematic review and network meta-analysis. Each study was created to discover the impact that LLLT has on reducing and relieving symptoms associated with the diagnosis of KOA.

RESULTS

Study Design: The articles in review demonstrated the efficacy of LLLT on symptom relief and management for individuals diagnosed with osteoarthritis of the knee.[2-3, 5-6] See Table 1 for supplemental information on the design of each study.

Jankaew et al[2] conducted a randomized, double-blinded controlled trial to compare the therapeutic effects of LLLT with 808 and 660nm wavelength on muscle strength and functional outcomes in individuals with OA of the knee. Throughout this study, 47 participants were randomly assigned into three groups: LLLT with a wavelength of 808nm, LLLT with a wavelength of 660nm, and the sham control group with LED red light. Two LLLT groups received continuous LLLT with an average power of 300mW in various wavelengths for 15-minute sessions occurring three days per week for eight weeks directed at the knee joint. The control group received the sham LED red light treatment. Three laser machines were set with the parameters and labeled with only numbers 1 to 3 before the experiment started ensuring both participants and examiner were blinded to the input settings of all machines. At baseline, knee strength and functional performance were analyzed by the 30-s sit-to-stand, 40m fast-paced walk, stair climbing, and the TUG test. Each of these tests was then again analyzed one week after interventions were completed to determine the efficacy of treatment for each group.

The study completed by Elboim-Gabyzon et al[3] conducted a comparison study examining laser therapy versus pulsed electromagnetic field therapy (PEMFT) as treatment modalities for early OA of the knee. This was a single-blinded (assessor) randomized, controlled trial that randomized participants to receive either pulsed electromagnetic field therapy or LLLT to compare the effects on pain and physical functions of participants with KOA. Forty participants with grade 2-3 KOA were randomized to receive select treatments for six sessions lasting 15 minutes per session over a 3-week period. To examine results and efficacy or treatment options, pain at rest, walking, standing from a sitting position, and climbing stairs were assessed using a visual analog scale. Functional level was measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), timed up-and-go test (RUG), and 10m walk (10MW) test. Each was obtained before and after interventions were completed.

Stausholm et al[5] conducted a systematic review and meta-analysis of randomized placebo-controlled trials involving participants with KOA according to the American College of Rheumatology and/or Kellgren/Lawrence (K/L) criteria. In each study included within the analysis, LLLT was applied to participants' knee(s) and self-reported pain, disability, and/or quality of life (QoL) was reported. While conducting their search 2,735 records were identified, however, only 22 met their search criteria and were included in the review.

Khalilizad et al[6] conducted a systematic review and network meta-analysis comparing the efficacy of combining exercise therapy (ET) with high-intensity laser therapy (HILT) versus LLLT on pain and function in KOA. This study was conducted due to numerous uncertainties regarding the magnitude of therapy needed to improve function while reducing pain in patients with KOA. In total, 11 RCTs were included within this analysis. To measure continuous data,

pain and function were assessed by using the visual analogue scale (VAS) pain score and the WOMAC, respectively.

Recruitment: Participants of studies conducted by Jankaew et al[2] and Elboim-Gabyzon et al[3] were recruited from the university hospital and local orthopedic clinics. Participants from the studies by Stausholm et al[5] and Khalilizad et al[6] and were from previously conducted studies that examined the effects of LLLT on pain relief by comparing different doses. See Table 2 for additional recruitment information.

Inclusion Criteria: The inclusion criteria among all studies were similar, specifically requiring a previous diagnosis of osteoarthritis of the knee.[2-3, 5-6] Additionally, the ability to ambulate independently, perform routine activities of daily living (ADLs), and experience symptomatic pain or disability relating to KOA were required for all studies.[2-3, 5-6] However, each study did have variability in their inclusion criteria. Jankaew et al[2] required the diagnosis of KOA to be completed by an orthopedic surgeon, while other studies required diagnosis by the American College of Rheumatology guidelines or the K/L classification system.[3,5] Elboim-Gabyzon et al[3] uniquely required a diagnosis of primary KOA, with secondary KOA being excluded from their study parameters. Khalilizad et al[6] only included RCTs that used adult subjects and examined the efficacy of using combination therapy, rather than laser therapy alone. See Table 2 for specific inclusion criteria for each analyzed article incorporated into this study.

Exclusion Criteria: Exclusion criteria had slight variance between studies. The exclusion criteria for Jankaew et al[2] included acute infectious diseases, abnormal blood pressure readings, cancer patients, pregnant patients, or coagulation disorders. The exclusion criteria for Elboim-Gabyzon et al[3] included a diagnosis of secondary KOA, rather than primary, uncontrolled diabetes, heart disease, and a BMI greater than 40. Similarly, these two studies both

excluded individuals with a pacemaker or other implantable device, sensory disturbances or paresthesia in the lower extremities, and patients with a previous history of lower limb surgery.[2,3] The study completed by Stausholm et al[5] excluded HILT trials, Narrow-Band Light Therapy (NBLT) trials, studies without a placebo-control group, nonspecific knee pain, and articles where the full-text was not available for review. The study conducted by Khalilizad et al[6] excluded numerous article types and/or study designs. See Table 2 for specific exclusion criteria for each analyzed article incorporated into this study.

Demographics: Participants in all studies were previously healthy individuals who had a prior diagnosis of KOA. Each RCT and meta-analysis of RCTs covered a wide variety of ages and varying ethnicities. Each study incorporated into this review did not expand on details regarding their patient population.

Pre-Participation Assessments: Participants selected for the Jankaew et al[2] study were assessed for lower extremity muscle strength and functional outcomes for the pre-intervention test. Then, the participants were randomized into groups and underwent the eight-week intervention program. The post-test was carried out following the same sequences as the pre-test. To prevent cross-over effects, all included participants were prohibited from engaging in other rehabilitation programs during the protocol period. Also, on the pre- and post-assessment day, the participants were requested to avoid alcohol and to refrain from caffeine and consumption of painkillers.

Two assessments were performed throughout the study conducted by Elboim-Gabyzon et al[3] to measure the outcomes of pain intensity and functional level. The first assessment was completed prior to treatment group allocation and the second at the end of the treatment sessions.

All assessments were performed by the same trained physiotherapist who was blinded to the treatment group allocation and was not involved in the interventional process.

For each meta-analysis of RCTs conducted by Stausholm et al[5] and Khalilizad et al[6] specific inclusion criteria were required prior to being accepted into the analysis. Specific testing for each RCT was not required prior to admission.

Study Treatment: The study conducted by Jankaew et al[2] assessed the efficacy of LLLT treatment for their patient population by having sessions three times per week for 8 weeks. Their study did not incorporate any additional exercises or other interventional methods. LLLT sessions were conducted, for each group, in a sitting position and performed directly at the knee joint. Each machine had 3 panels with 4 treatment spots/panels as inversed U shape to cover each knee joint and give the energy of 5.76 J. This dosage meets the recommended minimal dose by the World Association for Laser Therapy for knee OA. The minimum dosage recommended is ≥ 4J per treatment point for the 808nm wavelength with no current recommendation for the 660nm wavelength guideline. The joint line of each patient's knee was covered with 6 treatment spots. Patients within group 1 received LLLT (TI 816-8C-808, Transverse Industries Co.) with a wavelength of 808nm, with a mean power output of 300mW, for 15 minutes per session. Patients within group 2 received LLLT (TI 816-8C-660, Transverse Industries Co.) with a wavelength of 660nm, with a mean power output at 300mW, for 15 minutes per session. The sham control group received LED red light with a mean power output of 0.35mW and 0.0033J for 15 minutes per session with very limited photobiomodulation effects. The LLLT therapy was applied to the affected side or individually applied to each knee if participants were bilaterally affected. Each group was involved in their various treatment plan for 3 sessions per week for a duration of 8 weeks, totaling 24 sessions.

Elboim-Gabyzon et al[3] conducted a similar study, by randomly assigning participants to one of the two intervention groups using a computer-generated random allocation software sequence. Most of the participants included within this study had been diagnosed with grade 3 KOA (70%). Both PEMFT and LLLT were administered using a PhysioGo 500I device (Astar Company, Poland). The intervention was performed with the patient in the supine position with their knee supported in a 15-30 degree of flexion depending on the comfort and pain reported by the patient. Each treatment was administered for 6 sessions over a 3-week period. No additional treatment methods were used throughout this study; however, participants were instructed to continue with their usual daily activities. LLLT was performed with specific treatment parameters: power, 100% dose, 8 J/cm^2; frequency, 2 Hz; duty factor, 75%; and treatment area, $20cm^2$ applied over 5 points over the anterior part of the articular space for 3 minutes at each point for a total time of 15 minutes. PEMFT was focused over the medial and lateral sides of the knee following specific parameters: rectangular field shape; frequency, 20 Hz; intensity 10mT; and treatment time, 15 minutes.

Analysis of the RCTs was completed in the meta-analysis completed by Stausholm et al[5], discovering the mean K/L grades was 2.37 and the mean baseline pain was 63.61mm VAS (35.25-92). LLLT was used as an adjunct to exercise within 11 trials with the mean duration of the treatment periods of 3.53 weeks with the recommended LLLT dosage. Non-recommended LLLT doses were used in 9 trials with a mean duration of 3.7 weeks. The goal of this meta-analysis was to determine the efficacy of LLLT for pain reduction while comparing results for different dosage options for the treatment of KOA. Pain intensity was the primary outcome of this study.

Khalilizad et al[6] determined the standardized mean difference (SMD) with a 95% confidence interval (CI) by pooling continuous data extracted from individual studies on VAS and WOMAC using a random-effects model. Their analysis focused on data collected at four and eight weeks after the interventions began.

Methods of Measurement: Osteoarthritis Research Society Internation (OARSI), a 30-second chair stand test, a 40m fast-paced walk test, a stair climb test, and the timed up-and-go test are recommended as standard outcome measures among studies on this topic.[2] These exams are used to represent the daily physical activities and functional performance. The tests were performed three times for each performance test starting with the 30-second sit-to-stand test, the 40 m fast-paced walk test, the TUG test, and the stair climb test.[2] Jankaew et al[2] used this evaluation method to monitor and investigate the effectiveness of LLLT among KOA patients.

Functional level was assessed using the Hebrew version of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).[3] This was measured by two performance tests: timed up-and-go (TUG) and a 10m walk (10MW) test.[3]

The primary outcome of the meta-analysis was aimed to discover how LLLT affects pain intensity.[5] Pain was reported with continuous, numeric, and categorical/Likert scales that highly correlate with pain measured using the VAS. Scores of all pain scales were transformed to 0%-100% corresponding to 0-100nm VAS.[5] These results were combined with the mean difference (MD) method, using the change scores.[5] Level of disability was also assessed by allowing individuals to self-report their results. These results were synthesized with the standardized mean difference (SMD) method using change scores solely. The SMD was adjusted to Hedges' h and interpreted as follows: SMDs of 0.2, ~0.5, and >0.8 represent a small, moderate, and large effect, respectively.[5] The meta-analysis used two prespecified time points of assessment, including

immediately after the end of LLLT therapy and the last point of assessment 1-12 weeks after the end of LLLT during their follow-up.[5]

The systematic review and network meta-analysis completed by Khalilizad et al[6] was primarily completed to examine the efficiency of HILT or LLLT plus ET for KOA on pain and functional improvement. This was completed by pooling the continuous data on the VAS and WOMAC function score using a random-effects model. Currently, limited information regarding clinical efficiency of HILT or LLLT in conjunction with exercises for rehabilitating KOA have been conducted. This meta-analysis was completed to investigate and compare the relative effects of HILT versus LLLT combined with ET in alleviating pain and improving function in patients suffering from KOA at 4-week and 8-week follow-up intervals.

Safety and Ethical Consideration: Prior to the data collection in the study conducted by Jankaew et al[2], all patients were informed of the full treatment protocol and were required to sign an informed consent approved by the Institutional Review Board (IRB) of the National Cheng Kung University Hospital prior to beginning. The ethics protocol number was A-ER-109-187.[2] For the study completed by Elboim-Gabyzon et al[3], all participants were provided with written informed consent before participation. A detailed explanation of the study objectives and design was also provided to all individuals participating in the study.[3] The trial was registered in the ISRCTN registry (trial ID: ISRCTN17001174) and was performed by the Declaration of Helsinki.[3] The individual studies that were included in the analysis by Stausholm et al[5] and Khalilizad et al[6] required individual informed consent prior to the initial experiment. Patient consent was not required for publication of this meta-analysis.[5,6]

Statistical Methods: The randomized controlled trial conducted by Jankaew et al[2] used descriptive statistics to present the participants' characteristics. The Shapiro-Wilk test was used

to test the normality of the data, and a paired t test, or Wilcoxon signed-rank test, determined based on the result of normality of the data with $p>0.05$, which was used to compare the differences before and after the intervention in each group. Multivariate analysis of covariance (MANCOVA) was used to compare the differences among the three groups after the intervention, and the pre-assessment data was used as covariates to correct the post-assessment results. Cohen's d was computed to represent the magnitude of the effect size between groups differences. The statistical analysis was performed with SPSS version 22 (New York, USA) with significance set at $p<0.05$.

Stausholm et al[5] compared pre-intervention and baseline characteristics performed using the Chi-square test for sex, K/L grade, and side involved. The Wilcoxon two sample test was used to analyze BMI, pain set, and age. Changes in treatment effectiveness are presented as the difference between baseline and post-intervention values, termed delta. Time was analyzed separately using Friedman's Chi-square test, The magnitude of effect size was defined by Kendall's W value as 0.1-0.3, small effect; 0.3-0.5, moderate effect; and ≥ 0.5, large effect. Group effect was analyzed using the Wilcoxon two-sample t test alone with the Wilcoxon effect size test (R). The magnitude of effect was defined as 0.10- <0.3 for small effect, 0.3-0.5 for moderate effect; and ≥ 0.5 for a large effect. The Wilcoxon effect size test (R) was used to assess the effect size. Statistical significance was set at $p<0.05$.

Stausholm MB et al[5] used the software program Excel 2016 (Microsoft) and Review Manager Version V.5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The included trials were synthesized with meta-analyses and subgrouped by dose using the World Association for Laser Therapy treatment recommendations. Cochrane's risk-of-bias tool was used.

Khalilizad et al[6] began by transferring the electronic database search records to EndNote X8.1 (Thomson Reuters, Stamford, Connecticut, USA), reference management software. Pertinent information was extracted onto a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, Washington, USA) including author's name, publication year, irradiation parameters, exercise program, number of subjects, mean age, and study outcomes. Continuous data regarding mean and standard deviation on pain and functional improvement for three groups (LLLT +ET, HILT + ET, and placebo + ET) was analyzed. In cases where non-English reports were included, Google Translate was utilized, as necessary. Potential bias was assessed in RCTs included by using the updated Cochrane-risk-of-bias tool for randomized trials (RoB 2) and displayed the results using the robvis tool.

Statistical Analysis: The results of the study by Jankaew et al[2] identified that after the 8 week intervention period, improvements in strength of the knee extensor were found in the 808nm group only (+2.16%, $p<0.001$), while the strength of the extensor showed an increasing trend in the sham control group (+1.74%, $p=0.083$) and no change in the 606nm group (-0.36%, $p=0.82$). In addition to strengths outcomes after therapeutic intervention, functional outcomes were also assessed. An increase in the scores of the 30-second chair stand test were observed in the 660nm group only (+2.22 times, $p=0.006$), while the other two groups showed minimal improvement (+0.83 times and $p=0.35$ in the 808nm group and +0.58 times and $p=0.325$ in the sham control group). Decreases in the 40m fast-paced walking time, TUG time, and stair climbing time were significant in the 808nm group ($p=0.001$, 0.009, 0.003), 660nm group ($p=0.001$, 0.001, 0.003), and the sham control group ($p= 0.009$, 0.006, 0.001), respectively.

The results from the study completed by Elboim-Gabyzon et al[3] showed significant improvement in pain and physical function in both treatment groups. Pain intensity in all four

activities improved greatly for each group. However, the change of values before and after treatment was found to be significantly greater in three out of four activities in the PEMFT group, suggesting that PEMFT is more effective for relieving pain than LLLT. WOMAC scores (0-96) following intervention showed improvement in each, with greater from the PEMFT (72.5 pre-study to 53.3 post-study) group versus the LLLT group (72.2 pre-study to 62.4 post-study). Physical function was measured by a subscale of the WOMAC and the TUG test. Physical function was shown to have improved in each group, with significant treatment improvement in who that received PEMFT.

The results from the study Stausholm et al[5] showed that pain was significantly reduced using LLLT compared with the placebo control group at the end of therapy (14.23mm VAS (95% CI 7.31-21.14); I^2=93%; n=816; and during follow-ups 1-12 weeks later (15.92mm VAS (95% CI 6.47-25.37); I^2=93%; n=581). The subgroup analysis indicated that pain was also reduced by the non-recommended LLLT doses compared with placebo at the end of therapy (6.34 mm VAS (95% CI 1.26 to 11.41); I^2=44%; n=336) but the difference during follow-ups 1-12 weeks later was not significant (6.20 mm VAS (95% CI −0.65 to 13.05); I^2=38%; n=189). Overall, disability was significantly reduced by LLLT compared with placebo at the end of therapy (SMD=0.59 (95% CI 0.33 to 0.86); I^2=57%; n=617) and during follow-ups 1–12 weeks later (SMD=0.66 (95% CI 0.23 to 1.09); I^2=67%; n=289). The dose subgroup analyses demonstrated that disability was significantly reduced by the recommended LLLT doses compared with placebo at the end of therapy (SMD=0.75 (95% CI 0.46 to 1.03); I^2=34%; n=339) and during follow-ups 2–8 weeks later (SMD=1.31 (95% CI 0.92 to 1.69); I^2=0%; n=129). The between-subgroup differences in disability results were in favor of the recommended LLLT

doses over the non-recommended LLLT doses but only significantly regarding one of two-time points (p=0.11 and <0.0001).

The results from the network meta-analysis conducted by Khalilizad et al[6] showed that significant improvements in the VAS pain and WOMAC function scores on weeks 4 and 8 after interventions in groups treated with LLLT + ET and HILT + ET compared with placebo + ET. This analysis demonstrated a statistically significant reduction in the VAS pain score in week 4 in groups treated with HILT + ET (SMD = -1.01; 95% CI: -1.93 to -0.08; P-score = 0.87) and LLLT + ET (SMD = -0.64; 95% CI: -1.20 to -0.07; P-score = 0.62) compared with the control. There was moderate heterogeneity between the studies ($\tau^2 = 0.23$). Significant difference was observed in the VAS pain improvement between HILT + ET and LLLT + ET by week 4 (SMD = -0.37; 95% CI: -1.45 to 0.71; P-score = 0.77). In week 8, significant decreases were shown in the VAS pain scores in patients who received HILT + ET (SMD = -2.24; 95% CI: -2.85 to -1.63; P-score = 1.00) and LLLT + ET (SMD = -0.84; 95% CI: -1.27 to -0.40; P-score = 0.50) compared with the control. In conclusion, HILT + ET showed a greater improvement in the VAS pain compared with LLLT + ET by week 8 (SMD = -1.41; 95% CI: -2.05 to 0.76; P-score = 0.81).

DISCUSSION

The studies included in this review suggest that LLLT is a beneficial modality of treatment alone or in conjunction with additional therapies for pain relief and symptomatic management for individuals diagnosed with KOA. The study conducted by Jankaew et al[2] found that LLLT with 808 and 660nm wavelengths can improve knee muscle strength and function performance after 8 weeks of interventional treatment. The group treated with the 808nm wavelength exhibited superior effects compared to the other two groups on muscle strength.[2] This study concluded that LLLT should be recommended for use as a physical agent of

treatment, concomitantly with rehabilitation programs for symptom relief and management for individuals with KOA.[2] The trial completed by Elboim-Gabyzon et al[3] determined that both PEMFT and LLLT were effective in reducing pain while enhancing physical function in participants with diagnosed grades 2-3 primary KOA. The results concluded that PEMFT was shown to be more effective than LLLT in improving pain while resting, going from a sitting to a standing position, and while climbing stairs.[3] Stausholm et al[5] concluded that LLLT reduces pain and disability in KOA at 4-8J with 785nm wavelength at 1-3J and with 909nm wavelength per treatment spot.[5] The systematic review and meta-analysis conducted by Khalilizad et al[6] determined that HILT and LLLT in conjunction with ET has significant improvement on pain reduction and functional improvement. Ultimately, each groups showed positive effects on management of KOA in comparison to the placebo control group, with HILT + ET showing the most beneficial effects for treatment of KOA.[6] Overall, the results of each study support using LLLT as an effective treatment option for individuals with KOA for symptom relief and pain management.[2-3, 5-6]

Limitations amongst all studies were present and varied greatly between the three articles reviewed. The trial completed by Jankaew et al[2] describes how the required number of each intervention group used to detect the significant therapeutic effects (N=30) was greater than the number of enrolled participants in the study. Also, an isolated laser modality was implemented as a treatment within this study.[2] Based on current literature, combining laser with other treatments or exercise protocols may lead to better improvements in knee function.[2,6] The study conducted by Elboim-Gabyzon et al[3] did not summarize the patients' medications prior to performing the interventions and did not limit their use during the intervention period, which may have potentially affected the results. Lastly, long-term follow-up was not completed to monitor the

benefits of treatment modality.[2,3] Due to this, the long-term effects of the interventions are unable to be determined at this time. In each study, only included individuals with grades 2 and 3 KOA were accepted to participate, therefore, the results of the current studies cannot be generalized to individuals with KOA grade <2 or >4.[2,3] The trial completed by Stausholm et al[5] lacks QoL analysis, a detailed disability time-effect analysis and direct comparisons between LLLT and other interventions. A limitation of the meta-analysis completed by Khalilizad et al[6] was the absence of subgroup analysis based on follow-up periods. To overcome this, analysis was conducted in 4-week and 8-week interventions.[6] Additionally, this was a network meta-analysis, which could provide more precise estimates than traditional pairwise meta-analysis; with this analytic approach, this shows that HILT + ET was more efficient than LLLT + ET.[6]

A limitation of this review is that the length of duration and treatment using LLLT was inconsistent throughout all trials. Ideally, a comparison of different studies using the same timeframe would benefit results and expectations. Additionally, having studies that followed patients to discover long-term effects would benefit greatly. While the results are clinically relevant, they may not accurately represent the outcomes in patients using LLLT for symptomatic relief and pain management with a shorter duration of treatment time. Another limitation is the lack of evidence-based research currently available for review. A strength of this review is that all studies produced clinically meaningful outcomes that can applied to the treatment of chronic KOA management which positively affects millions of individuals worldwide.[1-6]

Review of the use of LLLT for symptomatic relief and pain reduction for individuals with diagnosed OA of the knee has shown favorable effects for patients. This review analyzed 2 RCTs and 2 meta-analyses evaluating the impact and efficacy of LLLT and symptom reduction of

KOA. Reports have shown significant positive effects for patients with KOA has been evaluated and reported significant by Jankaew et al[2], Elboim-Gabyzon et al[3], Stausholm et al[5], and Khalilizad et al[6] favoring the positive effects of using LLLT for symptomatic relief and pain management. Ultimately, this study supports the use of LLLT alone, or in conjunction with other treatment modalities, for individuals with mild to moderate KOA for reduction of pain, improvement of symptoms associated with disease, and improvement of overall QoL.[1-6]

Future research should be conducted to evaluate and determine the significance of symptom management and relief for individuals diagnosed with severe KOA. Most of the research currently available has primarily examined the beneficial effects for mild to moderate KOA. In addition, determining the minimum duration, length of therapy, and specific amplitude of wavelengths needed to show positive effects on patient outcomes should be determined.

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Table 1: Study Design

Author	**Study Type**	**Location**	**Length of Trial**	**Diagnosis**
Jankaew et al	RCT	North District Tainan, Taiwan	15-minute sessions 3x/week for 8 weeks	Osteoarthritis Research Society International (OARSI)
Elboim-Gabyzon et al	RCT	Israel	15-minute sessions x 6 sessions over a 3-week period	K/L criteria
Stausholm MB et al	Meta-Analysis of RCTs	Variable	Variable	American College of Rheumatology and/or K/L criteria
Khalilizad et al	Systematic Review and Meta-Analysis of RCTs	Variable	4-week or 8-week trials	VAS and/or WOMAC criteria

Kellgren/Lawrence (K/L)
Randomized Controlled Trial (RCT)
Visual Analogue Scale (VAS)
Western Ontario and McMaster Universities and Osteoarthritis Index (WOMAC)

Table 2: Participant Selection

Author	**Recruitment**	**Inclusion**	**Exclusion**
Jankaew et al	- 48 KOA participants were screened and recruited from the university hospital and local orthopedic clinics.	- Knee OA patients diagnosed by orthopedic surgeons in both genders (50-80 years old) with scale grades 2 and 3 - Experiencing knee pain ≥ 3 on visual analog scale (VAS, ranging from 0 to 10). - Able to walk on level ground and able to climb stairs without an assistive device or assistant	- Acute infectious diseases - Abnormal blood pressure or fever - Tumor or cancer patients - Pregnant - Special abnormalities or paresthesia's - Coagulation disorders - implantable devices (pacemakers, EKG machines, etc.) - Previous surgery in the knee or hip with

		- Not enrolled in intensive exercise or rehabilitation programs.	total or partial prosthesis
Elboim-Gabyzon et al	- 46 participants were recruited between May 15, 2021, and September 15, 2021, from an outpatient orthopedic clinic in Israel. - 40 of the 46 participants met the inclusion criteria and were included within the study. - Grade 2 (30%) - Grade 3 (70%)	- Diagnosed with primary KOA - Aged between 50 and 75 years - Symptomatic knee pain of 6 months of longer - Pain level ≥ 4 out of 10 according to the VAS - Independent walking ability of at least 30m - Grade 2 or 3 KOA according to the K/L classification scale	- Secondary KOA - Significant sensory disturbances in the lower extremities - Uncontrolled diabetes - Heart disease - BMI > 40 - Presence of a pacemaker - Previous history of lower limb surgery - Implants in the body - Inability to understand simple instructions
Stausholm MB et al	- 22 trials (n=1063) were meta-analyzed	- Randomized placebo-controlled trials - Specific knee pain - Diagnosis of KOA according to the American College of Rheumatology and/or K/L classification scale - LLLT applied to participants' knee (s) and self-reported pain, disability, and/or quality of life (QoL) was reported.	- High Intensity Laser Therapy (HILT) - No placebo-control - Full-Text not available - Non-Specific knee pain - No randomization - Narrow-Band Light Therapy (NBLT)
Khalilizad et al	- 11 articles were meta-analyzed - Sample sizes varied from 10 to 30 participants each	- RCTs - Studies that investigated the efficiency of HILT or LLLT alongside knee osteoarthritis ET in reducing pain and improving function of the knee.	- Review articles - Case reports - Editorials - Letters to the editors - Duplicate publications - Studies with data that could not be extracted on the specific outcomes

		- Adult population (aged ≥ 18 years old) with KOA - Interventions: HILT or LLLT plus ET - Outcomes: Pain reduction (based on the VAS) and/or functional improvement (based on the WOMAC)	

Exercise Therapy (ET)
High-Intensity Laser Therapy (HILT)
Low-Level Laser Therapy (LLLT)
Kellgren/Lawrence (K/L)
Knee Osteoarthritis (KOA)
Randomized Controlled trials (RCTs)
Visual Analogue Scale (VAS)
Western Ontario and McMaster Universities and Osteoarthritis Index (WOMAC)