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Review

Efficacy of High-Intensity Laser Therapy in Treating Knee Osteoarthritis: A First Systematic Review

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Abstract

Objective: The aim of this study was to evaluate the efficacy of high-intensity laser therapy (HILT) in the treatment of knee osteoarthritis (OA). ***Background:*** Due to increased number of randomized controlled trials evaluating efficiency of HILT in patients with knee OA, there was a need to present them in the form of systematic review. ***Methods:*** The search includes the databases as well as a manual search until August, 2017. The quality of the selected articles was determined in accordance with the revised guidelines of the CONSORT statement. ***Results:*** Six studies were included. Laser fluence ranged from 0.51 to 120 J/cm^2 for one treatment. The total energy transmitted during one treatment ranged from 1250 to 3000 J. All the selected studies found HILT to be beneficial in treatment of knee OA. ***Conclusions:*** HILT seems to be efficient in reducing pain and for providing functional improvements in patients with knee OA.

Keywords: efficacy, high-intensity laser therapy, knee osteoarthritis, systematic review

Introduction

Knee osteoarthritis (OA) is a chronic disease occurring mostly among older people.[1] Therefore, it is estimated that the problem of knee OA will be more serious in the future, because of aging population and other factors such as sedentary lifestyle and the increasing prevalence of obesity.[2] Knee OA can be associated with considerable physical disability, regardless of the type of affected joints. The most common symptoms of OA are inflammation and swelling of the synovia, which could lead to increased pain, stiffness, bone spurs, and restricted range of motion.[3] These symptoms impair functional status and quality of life.[4]

The conservative treatment forms for knee OA consist of pharmacological and nonpharmacological modalities. Nonsteroidal anti-inflammatory drugs are broadly used for pain relief and rigidity caused by OA. Nonetheless, they contribute to numerous side effects, particularly on the gastrointestinal tract, making the treatment unsustainable.[5] To reduce or eliminate these complications, nonpharmacological treatments have been utilized. Widely used nonpharmacological approaches include patient education, weight management strategies, kinesitherapy, manual therapy, orthotic devices,[2] and physical agent modalities such as electrotherapy, sonotherapy, and low-level laser therapy (LLLT).[6] The main purposes of the aforementioned treatments are pain reducing and improving functional status for a better quality of life.

In the past decade, high-intensity laser therapy (HILT) was implemented as a new form of therapy, but is not a routinely used treatment modality. HILT in these studies use neodymium-doped yttrium aluminum garnet lasers with high-peak-power (3 or 1 kW). The laser with the wavelength of 1064 nm induces slow light absorption by chromophores and transmits radiation into deep tissue to insure effectiveness of the therapy.[7] The benefit of HILT over LLLT is that HILT can stimulate deeper tissues, due to the higher output power.[8] Moreover HILT is recognized as a safe, painless, effective, and noninvasive treatment option.[9] Many researchers have shown the favorable impact of HILT in patients with different disorders such as knee OA,[10] subacromial impingement syndrome,[11] frozen shoulder,[12] osteoporosis,[13] chronic back pain,[14] and postburn pruritus.[15]

In the literature, there are increased number of randomized controlled trials (RCTs) evaluating efficiency of HILT in management of knee OA. Thus, they should be presented in the form of systematic review. Therefore, the purpose of our study was to assess, through a systematic review, the efficacy of HILT on pain reduction and functional improvement in patients with knee OA. The efficacy of this therapeutic modality was critically evaluated.

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Materials and Methods

Registration

This systematic review was recorded in PROSPERO under number CRD42017078308.

Focused question

We constructed our research question in accordance with the Participants, Interventions, Control, and Outcomes guidelines: ''Is HILT effective in treatment of knee OA?''

Literature search strategy

During August 2017, a systematic review of available literature was conducted by searching the databases PubMed, EBSCO, Science Direct, Springer, and Web of Science for RCTs that compared the effects of HILT with placebo, other forms of rehabilitation, or pharmacotherapy in patients with knee OA. In addition, a search of the published studies of references on the subject was carried out. No restrictions by publication period were used. The following keywords, individually or combined, were used: osteoarthritis, knee osteoarthritis, gonarthrosis, high-intensity laser therapy, high-intensity laser treatment, high-level laser therapy, HILT, HLLT, and high-power laser.

Study selection and eligibility criteria

Titles and abstracts of identified studies were assessed independently by two authors, and unsuitable studies were eliminated. Studies selected to the next step were then evaluated for inclusion. The following inclusion criteria were used: (i) access to the full content of the article; (ii) an eligible population of subjects with knee OA; (iii) the diagnosis of knee OA based on radiographic findings; (iv) HILT was used as an intervention in the treatment groups; (v) no restriction in the control groups that received other forms of rehabilitation, placebo, pharmacotherapy, or a lack of intervention; (vi) the study design used RCTs; (vii) clinical outcomes such as improvement of the functional status, pain alleviation, as well as gait analysis and ultrasonography were reported; and (viii) the article was written in English.

Review articles, case series, case reports, monographs, letters to the editor, conference reports, and unpublished data were excluded from the review.

Quality assessment

The quality of the selected studies was examined independently by two authors according to the revised guidelines of the CONSORT statement.[16,17] An overall assessment risk of bias as: (i) high—minimum one criterion was not met; (ii) moderate—minimum one criterion partly met, or (iii) low—all criteria met, was presented for each included study.

Data extraction, data analysis

The data were extracted from the selected studies independently by two authors, according to the following parameters: authors, study design, population, groups and sample sizes, mean age, interventions, outcome measurements, follow-up, type of laser, energy settings, treatment period, treatment area, and main outcomes. Data analysis was performed with a qualitative design. The initial purpose was to perform a meta-analysis, but we determined that this was not possible due to data inconsistencies and heterogeneity among the included studies.

Results

Study selection

Figure 1 presents the selection process for including studies in this systematic review. A total of 107 articles were initially identified. After removal of the duplicates ($n = 44$), a total of 63 articles were eligible for initial screening. After analysis of titles and abstracts, 50 of them were not relevant and thus omitted. Thirteen studies were included for thorough screening. Of these 13 articles, 7 articles were excluded

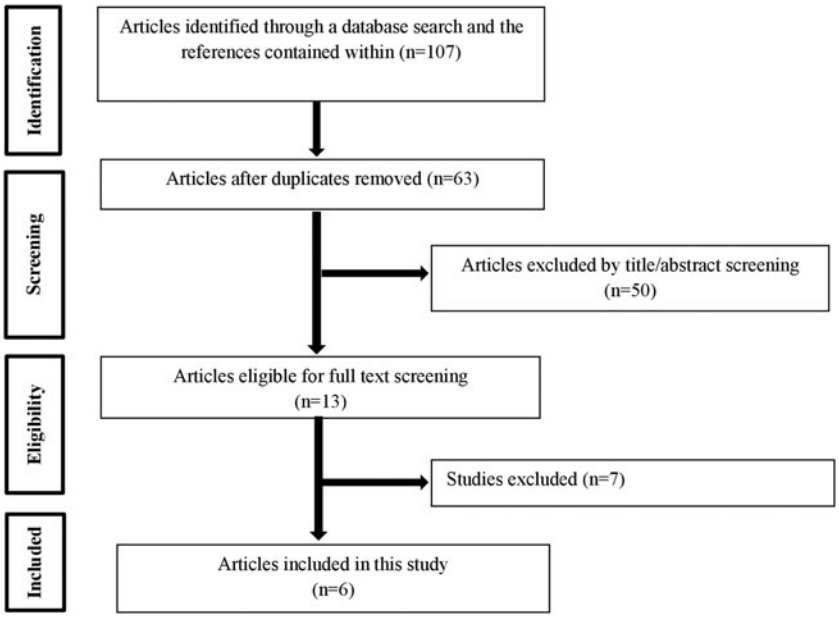

FIG. 1. A flowchart of the search strategy used to identify eligible studies.

because they did not meet the inclusion criteria (article in Russian language,[18] lack of full text,[19] case series,[20] article in Korean language,[21] lack of control group,[22,23] and article in Croatian language[24]). The remaining six articles were included in the final analysis.[10,25–29]

Characteristics of included studies

Study design, groups and sample sizes, types of intervention, outcome measurements, and follow-up of included articles are presented in Table 1. All studies were RCTs comparing the efficacy of HILT (exclusively or combined with other interventions) in management of knee OA with another type of therapy or placebo.[10,25–29] The intervention groups (HILT groups) consisted of 10–35 patients with mean age ranging from 52.1 to 70.5 years. Considering all six studies, 188 patients were submitted to HILT, and 207 subjects were considered as controls. The control groups were not treated similarly in the studies. Angelova and Ilieva[25] and also Gworys et al.[29] used a placebo sham laser as a comparison; Kheshie et al.[26] and Alayat et al. used placebo and exercises[10]; Alayat et al. included other control group that received exercises and glucosamine sulfate potassium chloride supplementation.[10] Kheshie et al. also examined a second control group that received LLLT and exercises,[26] and Gworys et al.[29] examined a second control group that received LLLT. In the study by Kim et al., the control group received conservative physical therapy,[27] and in study by Viliani et al., the control group received hyaluronic acid infiltrations.[28]

Patient status, a major endpoint for the studies, was measured by different methods: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC),[10,26–28] Fisher's dolorimeter and pedobarometric assessment,[25] ultrasonography,[10] Lequesne's Scale, and Laitinen questionnaire.[29] An analysis of subjective pain alleviation by using the visual analog scale (VAS) was included in all studies[10,25–27,29] with the exception of study by Viliani et al.[28]

Laser-related characteristics of included studies

Treatment protocol and laser parameters varied among studies and are summarized in Table 2. In five studies, lasers were used with a wavelength of 1064 nm,[10,25–28] in one there was two-wavelength laser (808 and 905 nm).[29] Energy density (fluence) ranged from 0.51 to 120 J/cm^2 for one treatment. The total energy transmitted to the patient's tissues during one session ranged from 1250 to 3000 J. In half of the studies included, there were 12 sessions of interventions,[10,26,27] in two studies, there were 10 sessions,[28,29] and the shortest session consisted of five treatments.[28] The treatment period varied from 1 to 6 weeks for each cycle and follow-up ranged from 1 to 4 months.

Main outcomes

In all studies assessing pain perception, HILT showed favorable results in pain alleviation compared with the control groups.[10,25–27,29] Also, a significant decrease in WOMAC was observed in studies.[10,25–28] Regardless of the treatment protocol used, interventions with HILT were more effective than the interventions in control groups[10,25–29] (Table 2).

Angelova and Ilieva[25] assessed the efficiency of HILT in treatment of knee OA. Seventy-two participants with clinically and radiographically determined knee OA were randomized into two groups: therapeutic (HILT, seven sessions of treatment) and control group (patients received sham laser). After 7 days of treatment, pain perception assessed by VAS and Fisher's dolorimeter decreased significantly in both groups in comparison with the baseline. The dynamics of pain alleviation was significantly greater in the subjects from the HILT group. Positive effects of therapy persisted also after 1 and 3 months. The results from the static and dynamic gait analysis indicated that only in participants from the HILT group, the difference in pressure under the heel and in the contact surface area (between the affected and unaffected leg) decreased significantly.[25]

Kheshie et al.[26] assessed the efficacy of HILT and LLLT on pain relief and functional improvement in patients with knee OA. Fifty-three male participants were randomized into three groups that received 12 sessions of HILT plus exercise, LLLT plus exercise, and placebo laser plus exercise. After 6 weeks of therapy, a significant decrease in VAS and WOMAC subscales was observed in all treatment groups. Authors showed also significant differences between pain level and WOMAC function subscale among all groups. Furthermore, HILT performed with kinesitherapy was more beneficial than LLLT with kinesitherapy, and both treatment modalities were more effective than kinesitherapy alone.[26]

Kim et al.[27] examined the effects of HILT on pain and function in patients with knee OA. Twenty subjects were randomly assigned into the HILT group (which received 12 sessions of HILT and conservative physical therapy [CPT]), and a control group (which received CPT). After 4 weeks of treatment, there were observed significant reductions in VAS and the WOMAC among both groups, in comparison with the baseline. Significantly lower scores in VAS and WOMAC were observed in HILT group than the control group.[27]

Alayat et al.[10] investigated the efficacy of HILT combined with glucosamine/chondroitin sulfate (GCS) in subjects with knee OA. Reduction in pain level, changes in knee function as well as synovial thickness (ST), and femoral cartilage thickness (FCT) were assessed. Sixty-seven participants were randomized into three groups: HILT group (treated with HILT GCS and exercises), a Comparison group I (treated with GCS plus exercises), and a Comparison group II (treated with placebo laser plus exercises). All groups received 12 sessions of treatment. After completion of the treatment program, significant reduction in VAS and WOMAC was observed in all groups. The authors have not found significant differences in VAS and WOMAC scores between sixth week of treatment and the third month of follow-up. After 6 weeks of treatment, significant reduction in ST among the HILT group, with nonsignificant decreases in the Comparison group I and Comparison group II as well as nonsignificant differences in medial and lateral FCT in all groups, was found.[10]

The aim of a study by Gworys et al.[29] was to assess the efficacy of different laser therapy programs in management of knee OA. Authors randomly assigned 125 patients to four groups: HILT group I was treated with two-wavelength laser (power 1100 mW, frequency 2000 Hz, energy density 6.21 J/cm^2); HILT group II received a similar program but with energy density 3.28 J/cm^2; Comparison group I was treated with one-wave laser (wavelength 810 nm, energy density 12.7 J/cm^2). Patients from the fourth group received

Table 1. Characteristics of the Included Studies and the Patients with Knee Osteoarthritis

Study	*Population*	*Groups sample size*	*Mean age ± SD*	*Interventions*	*The same interventions*	*Outcome measurements follow-up*
Angelova and Ilieva[25] Single-blinded RCT	Patients with a duration of symptoms for over 4 years, X-ray stages II, III grade by Kellgren and Lawrence classification of osteoarthritis	HILT group ($n=35$) Placebo group ($n=37$)	65.1 ± 1.40 64.7 ± 1.98	HILT Placebo laser	—	VAS Fisher's dolorimeter Pedobarometric assessment (static and dynamic analysis of gait) Follow-up after 1 month and 3 months
Kheshie et al.[26] Single-blinded RCT	Patients with a duration of symptoms for at least 6 months, knee osteoarthritis of grade II–III or less based on radiographic diagnosis of Kellgren and Lawrence	HILT group ($n=20$) Comparison group I ($n=18$) Comparison group II ($n=15$)	52.1 ± 6.47 56.5 ± 7.86 55.6 ± 11.02	HILT + ex LLLT + ex Placebo laser + ex	Patients in all treatment groups received an exercise program which consisted of active range of motion exercises, muscle strengthening, and flexibility exercises	VAS WOMAC Follow-up after 6 weeks
Kim et al.[27] RCT	Patients with knee osteoarthritis diagnosed based on clinical findings and X-ray images	HILT group ($n=10$) Comparison group ($n=10$)	65.3 ± 4.2 65.5 ± 4.0	HILT + CPT CPT	Patients in all treatment groups received conservative physical therapy, consisted of hot pack treatment for 20 min, interferential current therapy for 15 min, and deep heat diathermy	VAS WOMAC Follow-up after 1 month

(*continued*)

Table 1. (Continued)

Study	*Population*	*Groups sample size*	*Mean age ± SD*	*Interventions*	*The same interventions*	*Outcome measurements follow-up*
					using ultrasonic waves for 5 min	
Alayat et al.[10] Single-blinded RCT	Patients with knee osteoarthritis of grade III or less based on Kellgren and Lawrence classification, persistent pain for more than 3 months	HILT group ($n=23$) Comparison group I ($n=22$) Comparison group II ($n=22$)	55.0±4.41 53.6±3.54 52.8±5.03	HILT + GCS + ex GCS + ex Placebo laser + ex	The program included range of motion, flexibility, stretching, and strengthening exercises	VAS WOMAC Ultrasonography Follow-up after 6 weeks and 3 months
Gworys et al.[29]	Patients with a duration of symptoms for at least 6 weeks, knee osteoarthritic diagnosed based criteria established by the American College of Rheumatology	HILT group I ($n=30$) HILT group II ($n=30$) Comparison group I ($n=34$) Placebo group ($n=31$)	65.4±9.6 65.9±9 57.6±11.8 67.7±11.3	HILT HILT LLLT[a] Placebo laser	—	Lequesne's Scale Laitinen questionnaire VAS
Viliani et al.[28]	Patients with knee osteoarthritis of grade II or III based on Kellgren and Lawrence classification	HILT group I ($n=19$) HILT group II ($n=21$) Comparison group ($n=18$)	70.5 (range: 52–79) 69.6 (range: 51–72) 71.0 (range: 54–81)	HILT (10 sessions) HILT (five sessions) HA intraarticular infiltrations	—	WOMAC Follow-up after 4 months

CPT, conservative physical therapy (consisted of hot pack treatment for 20 min, interferential current therapy for 15 min, and deep heat diathermy using ultrasonic waves for 5 min); ex, exercises; GCS, patients received glucosamine sulfate potassium chloride (equivalent to glucosamine sulfate 500 mg) and chondroitin sulfate sodium (equivalent to chondroitin sulfate 400 mg) three times daily for 3 months; HA, four sessions of Hyaluronic acid infiltrations, molecular weight 500–1000 kDa, once a week; HILT, high-intensity laser therapy; LLLT, low-level laser therapy: GaAs laser GaAs, BTL-5000 laser, wavelength 830 nm, output power of 800 mW; RCT, randomized controlled trial. Average energy density of 50 J/cm^2, frequency of 1 kHz, duty cycle of 80%. A time of application of 32 min and 33 sec per session, a total energy of 1.250 J; LLLT[a], wave length 810 nm, dose 8 J/cm^2, surface density of energy 12.7 J/cm^2, power 400 mW in the continuous mode; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; SD, standard deviation.

Table 2. Laser Parameters of the Included Trials and the Effects of Treatment

Study	*Laser type*	*Energy settings*	*Treatment period (location of application)*	*Main outcomes*
Angelova and Ilieva[25]	Semiconductive neodymium laser IV produced by BTL, λ 1064 nm	First three sessions: 12 J/cm^2 = 300 J for treated area of 25 cm^2, 2 min, 25 Hz (analgesic effect). Next four sessions: 120 J/cm^2 = 3000 J for treated area of 25 cm^2, 10 min (biostimulating effect).	Seven sessions (single application per day). Sessions I–III applied on the medial and lateral sides of the knee. Sessions IV–VII applied on the medial side of the knee.	Pain levels at rest, on palpation and during movement measured by VAS and pain measured by dolorimetry decreased significantly in HILT group after 7 days of treatment (also at the follow-up 1 and 3 months later). Difference in pressure under the heel and in plantar contact surface area between the affected and unaffected leg decreased significantly only in the HILT group.
Kheshie et al.[26]	Nd:YAG laser by HIRO 3 device (ASA, Arcugnano, Vicenza, Italy), λ 1064 nm, maximal peak power 3 kW	The total energy during one session: 1250 J: in the initial phase 0.71 and 0.81 J/cm^2, total of 500 J; in the intermediate phase 0.61 J/cm^2, total of 250 J; in the final phase 0.71 and 0.81 J/cm^2, total of 500 J	Twelve sessions (two sessions/week for 6 weeks). Applied on the anterior, medial, and lateral aspects of the knee joint with emphasis on the application on the joint line between the tibial and femoral epicondyles.	HILT combined with exercises was more effective than LLLT combined with exercises (decreasing the VAS and WOMAC scores after 6 weeks of treatment). Both treatment modalities (HILT or LLLT) were better than exercises alone.
Kim et al.[27]	HILT device (HEALTRON, United Technology, Inc., Israel), λ 1064 nm	Intensity of the HILT was level 2, 11 Hz, total energy 1.5 J/cm^2, 5 min	Twelve sessions (three sessions/week for 4 weeks). Applied in the tibia and femoral epicondyle.	HILT group had statistically significant lower scores in both the VAS and the WOMAC than the comparison group.
Alayat et al.[10]	Nd:YAG laser by the HIRO 3.0 device (ASA, Arcugnano, Vicenza, Italy), λ 1064 nm, maximal peak power 3 kW	Initial phase and final phase applied in three steps. Every step 250 J. Level I: energy density of 1.43 J/cm^2, 30 Hz. Level II: energy density of 1.53 J/cm^2, 25 Hz. Level III: 1.78 J/cm^2, 20 Hz. Total energy of 1500 J was delivered on anterior and 1500 J on posterior knee surface. Total 3000 J.	Twelve sessions (two sessions/week for 6 weeks). Applied on anterior and posterior knee surface.	VAS and WOMAC were significantly decreased in all groups after 6 weeks, with nonsignificant differences between 6 weeks and 3 months of follow-up. Synovial thickness was significantly decreased in the HILT group posttreatment, with nonsignificant decreases in the Comparison group I and Comparison group II, as well as nonsignificant differences to femoral cartilage thickness in all groups. HILT combined with GCS and exercises was more effective than GCS + exercises and exercises alone.

(*continued*)

Table 2. (Continued)

Study	*Laser type*	*Energy settings*	*Treatment period (location of application)*	*Main outcomes*
Gworys et al.[29]	Pulsed (λ 905 nm)/ continuous (λ 808 nm) high power laser, MLS Laser Therapy	HILT group I: Power 1100 mW, 2000 Hz, energy density 6.21 J/cm^2. HILT group II: Power 1100 mW, 2000 Hz, energy density 3.28 J/cm^2.	Ten sessions (five sessions/week for 2 weeks). The knee was irradiated at 12 points: three points each at the level of the medial and lateral aspect of the knee joint gap, two points each at the level of the patellofemoral joint on the superior and inferior aspect of the joint, and two points in the popliteal fossa.	Statistically significant improvements in knee joint function according to Lequesne's scale were observed in all groups except the Placebo group. Statistically significant pain relief assessed with the Laitinen questionnaire and VAS scale was seen in all groups except the Placebo group. When Comparison group I, HILT group I and HILT group II were compared, the largest improvement was found in HILT group I (MLS laser, energy density 6.21 J/cm^2). The degrees of improvement in Comparison group I and HILT group II were similar.
Viliani et al.[28]	Pulsed high power laser, Nd:YAG, λ 1064 nm	The total energy during one session: 2000–3000 J. One session was implemented in three phases (initial, intermediate and final phase). Every phase was implemented in subphases in which increasing fluence (0.51–0.71 J/cm^2) and decreasing frequency (15–10 Hz) was administered.	HILT group I: 10 sessions (on alternate days). HILT group II: Five sessions (on alternate days).	Immediately after completion of the study, the three groups showed improvement in WOMAC. The greatest improvement was observed in HILT group I (WOMAC values decreased from 42.9 $\pm$ 7.3 to 21.4 $\pm$ 4). At follow-up (4 months) HILT group I and Comparison group maintained the improvement, while HILT group II showed a little regression of WOMAC values.

GCS, patients received glucosamine sulfate potassium chloride; LLLT, low-level laser therapy; MLS, multiwave locked system; Nd:YAG laser, neodymium-doped yttrium aluminum garnet laser; λ, wavelength.

sham laser. Significant decrease in Lequesne, Laitinen questionnaire, and VAS was found in all groups except the Placebo group. When Comparison group I, HILT group I, and HILT group II were compared, the greatest improvement was observed in HILT group I. The level of improvement in Comparison group I and HILT group II was similar.[29]

Viliani et al.[28] assessed the effects of two various HILT protocols in patients with knee OA. Fifty-eight patients were randomly selected and placed into three groups: HILT group I received 10 sessions of HILT (the total energy during one session: 2000–3000 J, fluence from 0.51–0.71 J/cm^2); HILT group II received the same program as HILT group I, but in five sessions; Comparison group received four sessions of hyaluronic acid infiltrations (once per week). All groups showed improvement in WOMAC immediately after completion of the treatment. The greatest improvement was observed in HILT group I (WOMAC values decreased from 42.9 ± 7.3 to 21.4 ± 4). After 4 months, HILT group I and Comparison group maintained the improvement, while HILT group II showed a slight worsening in WOMAC scale. No treatment side effects were recorded in any groups.[28]

Quality of the included studies

The outcomes of the CONSORT-based quality assessment are presented in Table 3. One study was at low,[26] one at moderate,[10] and four at high risk of bias.[25,27–29] The most common unmet criteria were the lack of a sample size estimation (criterion A), unreported completeness of follow-up (criterion D), and incomplete masking (criterion F).

Discussion

HILT is a recent rehabilitation therapy successfully used in diseases and injuries of the musculoskeletal system due to its fast effects, rapid relief of pain, and reduction of recovery time. In this study, a systematic review was conducted to assess the efficacy of HILT in patients with knee OA. A thorough systematic review of the selected articles indicated that HILT was efficient in management of knee OA.

The primary outcome analyzed in our systematic review was the pain reduction in patients with knee OA. Five studies selected to this review have used VAS to determine pain changes.[10,25–27,29] Results of our review indicated that HILT provides efficient pain relief in patients with knee OA. The secondary outcome connected with the HILT in knee OA was functional improvement, manifested by a decreased WOMAC scores. The above effects can be explained by the influence of laser on tissues. It has been reported that HILT reduces inflammatory process and the symptoms of pain. Potential mechanisms of analgesic and anti-inflammatory effects due to laser therapy are still unknown.[30,31] The effectiveness of HILT is thought to be a result of the specific and characteristic high-peak power of the laser pulse (up to 3 kW), with a relatively low frequency and pulse width. Thanks to this high-peak power, a large amount of energy is supplied for a short time, decreasing thermal accumulation phenomena. Thus, HILT is able to generate photothermal and photochemical effects in deep tissue.[15] These photochemical and photothermal effects may increase collagen production within the tissues and improve blood flow, cell metabolism, and vascular permeability, helping to decrease pain and repair damaged tissues.[32,33] Furthermore, a high-intensity laser pulse leads to slow light absorption via chromophores. This improves mitochondrial oxidative reactions and increases ATP, RNA, or DNA production.[9] The pain reduction after HILT is associated with multiple mechanisms, including an ability to increase the production of morphine-mimetic substances in the body and to inhibit the transmission of the pain impulses.[34]

The effectiveness of laser therapy is associated not only with different factors such as power output, fluence, wavelength, duration of therapy, the mode of operation but also with the optical properties of the tissue. Among the abovementioned factors, dose of laser is of paramount importance. In the studies included in this review, HILT dosage was variable (energy density ranged from 0.51 to 120 J/cm^2; the total energy from 1250 to 3000 J).[10,25–29] Due to the variety in the laser operation parameters, an optimal dose has not yet been determined. Wavelength is also regarded as relevant parameter for favorable results of laser therapy and has an impact on the depth of penetration through the tissues. It is known that laser radiation with a wavelength range from 700 to 1000 nm represents the near-infrared therapeutic window of transmission for deep tissue penetration, and this range of wavelength is commonly used in clinical treatment.

In the present review, we have found that the effect of HILT exclusively or combined with exercises, pharmacotherapy, or conservative physical therapy was greater than that of placebo laser, and other forms of physiotherapy or pharmacotherapy. In fact, LLLT, exercises, thermotherapy, diathermy, interferential current, and GCS were also efficient in reducing pain and improving functional status, but the interventions with HILT were more efficient. It has also been demonstrated that HILT in combination with GCS and kinesitherapy was effective in decreasing synovial thickening, which indicates that HILT has an anti-inflammatory effect on the synovium in OA.[10] Laser therapy reduces inflammation by altering prostaglandin synthesis and decreasing interleukin 1, C-reactive protein, and neopterin levels.[10,35] Therefore, suitable laser penetration through tissues has analgesic effect and activates the physiological reactions necessary to decrease inflammatory process and stimulate tissue healing.[36]

The results of one study included in our review showed nonsignificant differences in medial and lateral FCT after interventions in all treatment groups. The authors claimed that despite a minor increase in FCT, the significance was limited by insufficient sample size, the use of oral (instead of injectable) GCS, knee OA grades (I–III) that have been included in study, and a short period of follow-up (3 months). Despite the fact that the results were not statistically significant, a tendency toward improvement was noticed in the ultrasonography examinations. Assessment of FCT after 6 months was suggested in an additional follow-up.[10]

The assessment of the effectiveness of HILT is possible only in case of implementing studies with high scientific rigor. In our review, a careful selection of the literature was conducted, and articles that did not meet the inclusion criteria were eliminated. Six articles that met eligibility criteria were included in this review. CONSORT-based quality assessment of the selected articles indicated a high risk of bias in four of the six studies.[25,27–29] A main weakness was that four of the studies had failed to calculate the sample size, failed to report the completion of a follow-up, and did not

Table 3. CONSORT-Based Quality Analysis of the Included Studies

Category	*Description*	*Grading*	*Angelova and Ilieva*[25]	*Kheshie et al.*[26]	*Kim et al.*[27]	*Alayat et al.*[10]	*Gworys et al.*[29]	*Viliani et al.*[28]
A	Sample size calculation, estimating the minimum number of participants required to detect a significant difference among compared groups	0 = Did not exist/not mentioned/not clear 1 = Reported but not confirmed 2 = Reported and confirmed	0	2	0	1	0	0
B	Randomization and allocation concealment methods	0 = Clearly inadequate 1 = Possibly adequate 2 = Clearly adequate	2	2	1	2	1	1
C	Clear definition of inclusion and/or exclusion criteria	0 = No 1 = Yes	1	1	0	1	1	1
D	Completeness of follow-up (specified reasons for withdrawals and dropouts in each study group)	0 = No/not mentioned/not clear 1 = Yes/no withdrawals or dropouts occurred	0	1	0	1	0	0
E	Experimental and control groups comparable at study baseline for important prognostic factors	0 = No 1 = Unclear/possibly not comparable for one or more important prognostic factors 2 = Clearly adequate	2	2	1	2	1	1
F	Presence of masking	0 = No 1 = Unclear/not complete 2 = Yes	1	2	0	1	1	0
G	Appropriate statistical analysis	0 = No 1 = Unclear/possibly not the best method applied 2 = Yes	2	2	1	2	2	1
Estimated risk of bias			High	Low	High	Moderate	High	High

specify causes for withdrawals and dropouts in treatment groups.[25,27–29] Furthermore, no blinding or incomplete blinding of outcome assessment could have an impact on observed outcomes in included studies.[10,25,27–29] The above-mentioned methodological deficiencies would be recognized as a limitation to verify the efficacy of HILT in knee OA treatment, therefore, the results of this review should be carefully considered.

Overall, results of our review showed that HILT was superior to other forms of rehabilitation in terms of improving the pain reduction and functional status improvement in patients with OA. Although it was not assessed in this study, HILT is generally considered to be safe and none of the studies included reported any treatment side effects. However, due to the diversity of studies design and different treatment protocols in the reviewed studies, the outcomes of this review should be interpreted carefully.

This systematic review is not without limitations. The relatively small number of selected studies can be considered as a study limitation. The selected studies were methodologically different, the treatment protocol and parameters used in each study differed from each other. Due to the reported heterogeneity, conducting a meta-analysis was not possible.

Recommendations

Future studies should define the optimal dosages and treatment protocol of HILT in patients with knee OA. There are no recommendations from the World Association of Laser Therapy concerning high-intensity laser dosage for patients with knee OA for optimal treatment. After determining an accurate effective dose and delivery technique, future studies should compare HILT to other therapeutic modalities. The longest follow-up period (4 months) in the included studies was reported by Viliani et al.[28] Taken together, the evidence for long-term efficacy of HILT in patients with knee OA is not sufficient. Therefore, further randomized, high methodological quality studies with long follow-up (at least 6 months) are needed.

Conclusions and Summary

Overall, the results obtained from the present study suggest that HILT is efficient in reducing pain and for providing functional improvements in patients with knee OA. However, the CONSORT-based quality assessment of the selected studies indicated a high risk of bias in four of the six studies; therefore, further studies with high scientific rigor are required to clarify the best treatment protocol and the long-term results.

Author Disclosure Statement

No competing financial interests exist.

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