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Review Article

High-intensity laser therapy on pain relief in symptomatic knee osteoarthritis: A systematic review and meta-analysis

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Abstract.
BACKGROUND: Osteoarthritis is one of the leading causes of global disability and pain.
OBJECTIVE: To investigate whether High-Intensity Laser therapy has superior pain-relieving effects in individuals with symptomatic knee osteoarthritis.
METHODS: Searches were conducted using CENTRAL, MEDLINE, CINAHL, EMBASE, Web of Science, PEDro, and related reference lists with language limed to English. Clinical trials investigating the effectiveness of High-Intensity Laser therapy compared to other laser therapies, conventional therapies or exercises on knee osteoarthritis pain were included. The screening and selection of studies, data extraction, and methodological quality assessment were performed by two independent researchers. Studies were quantitatively integrated using the Review Manager Software and qualitative analysis using the criteria recommended by the Cochrane Collaboration.
RESULTS: Nine studies meeting the eligibility criteria were identified, among which only one study was identified as excellent methodology quality, six was marked as good quality, and the remaining two studies were regarded as fair or poor quality. All studies reported positive effects of High-Intensity Laser therapy on knee osteoarthritis pain. Two studies (136 people) gave indication that there was moderate evidence that High-Intensity Laser therapy could be a promising new possibility in pain relief among patients with knee osteoarthritis compared with sham laser therapy in a short-term treatment (MD, -2.04, 95% CI, -2.12 to -1.96; $Z = 51.01$, $P < 0.01$). Four studies (160 people) showed that High-Intensity Laser therapy could be an effective modality on treating pain compared to conventional physiotherapies in decreasing visual analog scale score (MD, -0.98, 95% CI, -1.19 to -0.76; $Z = 9.02$, $P < 0.01$). Three studies (123 people) demonstrated that High-Intensity Laser therapy combined with exercises was more effective than placebo laser or lower-intensity laser combined with exercises in alleviating pain in patients with knee osteoarthritis (MD, -1.54, 95% CI, -1.84 to -1.24; $Z = 10.06$, $P < 0.01$).
CONCLUSION: High-Intensity Laser therapy could be a promising and recommended modality in alleviating knee osteoarthritis pain, especially when it was implemented in combination with exercises.

Keywords: Laser therapy, knee osteoarthritis, pain, rehabilitation

1. Introduction

Osteoarthritis is one of the leading causes of global disability and pain [1–4] and a key symptom of individuals seeking medical care [5,6] and absenteeism [7,8] worldwide, especially in an aging [9,10] and predisposing obese group [11,12]. Knee osteoarthritis (KOA) is

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the most common form of osteoarthritis [13], accounting for more than four-fifths overall burden of the disease [14], characterized by structural alternations of the hyaline articular cartilage, subchondral bone, ligaments, capsule, and synovium [2].

Globally, the prevalence of symptomatic KOA was estimated to be 3.8% compared to hip osteoarthritis (0.85%) in 2010, peaking at around 50 years of age [1]. Statistically, knee and hip osteoarthritis were ranked as the 11th highest contributor to global disability measured by years of life lived with disability [1,2]. Pain is the most common complaining condition in people with KOA [2,15], followed by morning stiffness, restricted range of motion [2], joint buckling, swelling, muscle weakness, pain-related distress, functional limitations, and bony enlargement, resulting considerable impacts on activities of daily living [1], quality of life [7], occupation [8], leisure activities as well as sleep, which currently, are also the standard of diagnosing KOA.

There is a wide spectrum of factors associated with KOA, including age [16,17], gender [2,6], obesity [11,12], genetics [18], previous knee trauma [19], BMI [11,12], knee malalignment [20], and quadriceps muscle strength [21]. Consequently, management of these predisposed or highly risk factor seems to be highly essential, however, among which some features cannot be reversed or ameliorated in a short term, like age, gene, sex, distorted cartilage, or ligaments degeneration. Considering this, attention should be paid to the patient's pain relief or risk prevention such as balance issues and falls caused by KOA, particularly when pain extremely affects ambulation and sleeping [22].

Clinically, education, individual-specific exercise therapy (ET) as well as weight-loss are identified to be the first-line treatment in the long-term exercise protocol [23]. Nonetheless, therapeutic intensity and its effectiveness possibly be affected as pain initials drastically and the long-term adherence to ET and negative belief in patients with KOA are also barriers [24–26]. Therefore, the management of pain related to KOA is indispensable.

High-Intensity Laser therapy (HILT), is a promising option of treatment modality, which can penetrate deeper tissues (up to 100 mm) [27,28] than other laser therapies, playing a role in intraarticular of the knee, and being regarded as a noninvasive, safe, and effective method to treat pain. Previous studies demonstrated that HILT is effective in the management of Patellofemoral Pain Syndrome [29], subacromial syndrome [30], and low back pain [31], mainly because of its accelerating connective tissue repair, affecting fibroblast function, releasing of anti-inflammatory and endogenous mediators [32], as well as stimulating deeper soft tissue metabolism [33]. Recently, several studies utilizing varied protocols, were conducted to investigate the effectiveness of HILT in individuals with KOA. A similar meta-analysis published in 2020 by Hyun-Jin Song [34] did not divide the control group into separate groups and directly integrated quantitatively, which may exaggerate or reduce the effect of HILT on KOA pain. Consequently, the purpose of this study was to update the review related to the effectiveness of HILT on pain in individuals with KOA based on the types of the control group and provides recommendations on the decision-making process of managing KOA pain when choosing laser therapy or other physiotherapies.

2. Methods

2.1. Protocol and registration

This study was conducted based on PRISMA [35] (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and registered in PROSPERO (Registration Number: CRD42020175318).

2.2. Eligibility criteria

All eligible and published clinical randomized controlled trials, investigating the effectiveness of HILT on KOA pain, were included with language limited to English. Patients, 45 years of age or older, diagnosed as symptomatic KOA according to the American College of Rheumatology (ACR) classification, orthopedics, or rheumatologists' opinions, clinical or imaging findings. Studies, comparing all kinds of HILT (parameters including different wavelengths and power) to other treatments including placebo laser therapy (PL), ET, and conventional physiotherapies (CPT) were included. Participants with severe cognitive impairment or combined with other knee joint impairments were excluded.

2.3. Search strategy

Eligible articles were identified with key words ("knee osteoarthritis", "knee degenerative arthritis", "knee arthrosis", "knee OA" OR "KOA") AND ("high intensity laser therapy", "high power laser therapy", "HILT" OR "Nd: YAG"), utilizing the following databases. Electronic retrieval: CENTRAL (Cochrane Central Register of Controlled Trials, up to September

Table 1
Level of evidence

Level of evidence	Indications
Strong evidence	Consistent findings among multiple higher-quality RCTs
Moderate evidence	Consistent findings among multiple lower quality RCTs and/or one higher quality RCT
Conflicting evidence	One lower quality RCT
No evidence	No RCTs

2022), MEDLINE (1950 to September 2022), CINAHL (1982 to September 2022), EMBASE (1980 to September 2022), WOS (Web of science, 1900 to September 2022), PEDro (Physiotherapy Evidence Database, 1999 to September 2022), PsycINFO (1806 to September 2022), SCOPUS (2004 to September 2022). Manual retrieval: 1) manually retrieve references from relevant reviews and originally selected articles to include eligible studies; 2) manual search clinical trial registration platform: ClinicalTrials.gov.

2.4. Study selection

The screening and selection of studies were conducted by two independent researchers (WWY, CP) with authors and press unblinded. Afterward the studies were excluded if the titles and abstracts did not meet the pre-set standards. The consensus was achieved by discussion when it was unclear whether the controversial studies should be included, if controversy persists, a decision was made by group discussion (WWY, CP, CCX). Afterwards, the full text of studies originally selected was screened. A forward and backward search was conducted on these eligible studies using the Science Citation Index to obtain other relevant RCTs. Reasons for exclusion of the literature from the full text screening were recorded in the screening form.

2.5. Data extraction

Two reviewers (CP, WWY) independently extracted usable information, which contained the first author, publication date, participants' data (sample size, duration of symptom, and average age), interventions, outcome measurements, the term of follow-ups, from eligible studies.

2.6. Assessment of methodological quality

PEDro scale was performed by two independent researchers (CP, WWY) to evaluate the methodological quality of each eligible RCT (9–10: excellent, 6–8: good, 4–5: fair, and $\leqslant$ 4: poor), which consisted of 11 aspects (1: eligibility criteria were specified, 2: subjects were randomly allocated to groups, 3: allocation was concealed, 4: the groups were similar at baseline regarding the most important prognostic indicators, 5: there was blinding of all subjects, 6: there was blinding of all therapists, 7: there was blinding of all assessors, 8: measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups, 9: all subjects for whom outcome measures were available received the treatment or control condition as allocated, 10: the results of between-group statistical comparisons are reported for at least one key outcome, 11: the study provides both point measures and measures of variability for at least one key outcome). Each item was evaluated as 'yes' or 'no' according to whether it met the criteria, and "Item 1" was not considered in calculation of total score.

2.7. Data analysis

Extracted data was processed by Review Manager Software (version 5.30), with continuous variables were analyzed in the form of mean with a 95% confidence interval (CI). I^2 and Q test was used to calculate heterogeneity between studies in each group. I^2 greater than 50% or $P < 0.1$ was considered to have a greater heterogeneity [36]. Then, subgroup analysis (grouping according to different control groups) aimed at the source of heterogeneity, was performed. The random effects model was considered if the source of heterogeneity was not identified, compared to fixed-effect model in studies with no significant heterogeneity where $I^2 < 50\%$ and $P < 0.1$. Qualitative analysis was carried out by determining the level of evidence of pain relief improvement treated by HILT with original studies' methodological quality considered because of clinical heterogeneity, lack of data, etc., with interventions divided into three groups (HILT versus other laser therapies, HILT versus CPT, HILT + ET versus other therapies + ET), using the criterion recommended by the Cochrane Collaboration [37] (Table 1).

3. Results

3.1. Literature search

A total of 127 citations were brought into screening (Fig. 1). Then, 55 remained citations were screened

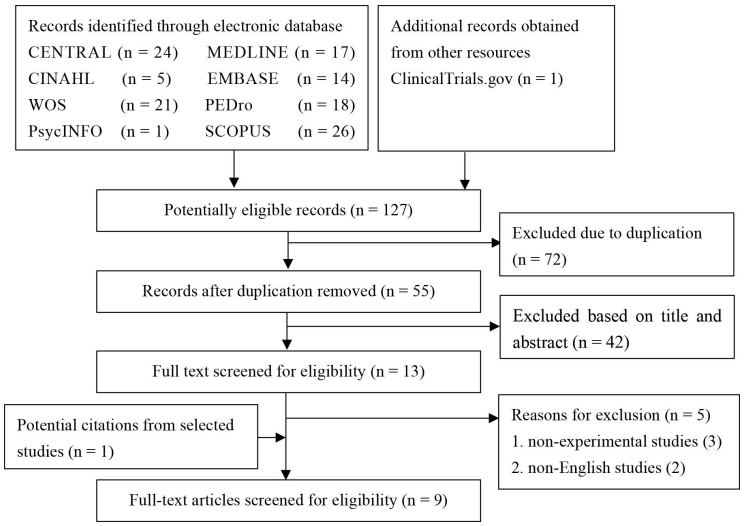

Fig. 1. Flow chart showing the screening process and search results.

for titles and abstracts after duplicate articles were removed with 13 articles remaining for full-text screening. Five articles were excluded after screening the full text among which two articles were in non-English language [38,39], and three articles [40–42] were only compared before and after treatment but not with other interventions. Finally, 9 articles [25,26,43–49] meet our selection criteria were included for the current review.

3.2. Study characteristics

A total of 9 studies [25,26,43–49] (419 people) meeting the eligibility criteria were identified to further analysis with sample size ranging from 20 to 125 (Table 2). The people included in this review were all diagnosed with KOA, but the diagnostic methods and duration of symptoms were not the same. Alayat et al. [43], and Kheshie et al. [46] diagnosed KOA based on expert opinions (orthopedics or rheumatologists) combined with the imaging findings of the knee joint, while Angelova et al. [44] and Kim et al. [47] mainly based on clinical findings (with or without imaging). The remaining 5 studies [25,26,45,48,49] were based on the American College of Rheumatology (ACR) classification criteria for the diagnosis of KOA. Regarding the duration of KOA, four studies [25,26,45,46] included people with a disease course of more than 6 months, one study [48] was more than 6 weeks, two [43,49] was more than 3 months, and the other [44] was more than 4 years. One study [47] included patients whose disease course was unknown. In 7 studies [25,26,43–46,49], the arthritis classification was at grade II or III (assessed by Kellgren and Lawrence classification), but the KOA classification of the subjects in the study of Gworys et al. [48] and Kim et al. [47] was unclear. The average age of the subjects in all studies was between 50 and 70.

In terms of the type of HILT, the dose, the treatment time, and the operation methods were different in individual studies (details were illustrated in Table 3). There were two studies [44,48] comparing HILT with other laser treatments (placebo laser, PL, LILT), 4 studies [26,45,47,49] comparing HILT with other therapies (CPT, ET), and 3 studies [25,44,46] comparing HILT + ET versus other laser treatments + ET with treatment sessions between 7–12 times.

For outcome measurements, the visual analog scale (VAS) was used in all 9 studies to evaluate pain intensity before and after operation.

3.3. Methodological quality

Of those 9 articles [25,26,43–49], only one study [25] was identified as excellent methodology quality due to the potential biases existed in the process of allocation concealment and assessor operation (Table 4). Six [26,43–46,49] of 9 were considered as having good quality, among which selection bias, attrition bias and performance bias were emerged separately or combined. The remaining studies [47,48] were regarded as fair or poor quality.

3.4. Effects on pain relief

HILT versus other laser therapies (PL, LILT)

There were two studies [44,48] comparing the effects

Table 2
Characteristics of included studies

Study ID	Population					Interventions		Outcome measures	Results
	Number Exp/Con	Age M (SD)	BMI Kg/m^2	X-ray stage	Duration of symptoms	Exp group Con groups	Treatment sessions		
Alayat 2017	23	55 (4.41)	28.15 (1.72)	$\leqslant$ III	$>$ 3 months	HILT + ET	12	VAS	VAS (6 W, 12 W follow-up): $P < 0.0001$
	22	53.64 (3.54)	28.91 (0.49)	$\leqslant$/III		ET	12		
	22	52.86 (5.03)	28.63 (1.00)	$\leqslant$/III		PL + ET	12		
Anna 2016	37	65.11 (1.40)	NA	II/III	$>$ 4 years	HILT	7	VAS	VAS (7 days): $P < 0.001$
	35	64.71 (1.98)	NA	II/III		PL	7		
Nazari 2018	30	61.5 (3.9)	27.7 (1.4)	II/III	$>$ 6 months	HILT	12	VAS	VAS (4 W, 12 W follow-up): $P < 0.001$
	30	62.4 (3.14)	27.2 (1.6)	II/III		CPT	12		
	30	62.24 (3.87)	27.5 (1.8)	II/III		ET	12		
Kheshie 2014	20	52.1 (6.47)	29.94 (3.36)	$\leqslant$ III	$>$ 6 months	HILT + ET	12	VAS	VAS (6 W): $P < 0.0001$
	18	56.56 (7.86)	28.62 (5.20)	$\leqslant$ III		LILT + ET	12		
	15	55.6 (11.02)	28.51 (3.35)	$\leqslant$ III		PL + ET	12		
Gworys 2012	30	65.4 (9.6)	NA	NA	$>$ 6 weeks	HILT	10	VAS	VAS (HILT vs PL): $P < 0.05$
	30	65.9 (9.0)	NA	NA		HILT*	10		VAS (HILT vs LILL): non-significant
	34	57.6 (11.8)	NA	NA		LILT	10		
	31	67.7 (11.3)	NA	NA		PL	10		
Kim 2016	10	65.3 (4.2)	NA	NA	NA	HILT	12	VAS	VAS: $P < 0.01$
	10	65.5 (4.0)	NA	NA		CPT	12		
Mazlum 2020	20	57.85 (8.06)	29.94 (5.49)	II/III	$>$ 6 months	HILT + ET	10	VAS	VAS (2 W, 6 W follow-up): $P < 0.05$
	20	58.62 (11.28)	31.95 (4.86)	II/III		PL + ET	10		
Mostafa 2022	20	46.62 (8.68)	29.26 (2.48)	II	$>$ 3 months	HILT	12	VAS	VAS (4 W): $P < 0.05$
	20	40.12 (9.45)	28.82 (5.23)	II		ESWT	4		
Samaan 2022	20	55.4 (6.34)	28.98 (2.23)	II/III	$>$ 6 months	HILT + ET	10	VAS	VAS (4 W): $P < 0.05$
	20	55.2 (4.77)	29.1 (2.42)	II/III		LIPUS + ET	10		
	20	57.0 (6.39)	29.75 (2.12)	II/III		ET	10		

NA: not available; HILT*: half the amount of HILT; VAS: visual analog scale; ET: exercise therapies; PL: placebo laser therapies; CPT: conventional therapies; W: weeks; ESWT: extracorporeal shock wave therapy; LIPUS: low-intensity pulsed ultrasound.

Table 3
Types of interventions of included studies

Study ID	Parameters of high intensity laser			Treatment sites	Application protocols	Comparators
	Types of HILT	Output power	Total dose			
Alayat 2017	Pulsed Nd: YAG laser produced by the HIRO 3.0 device (ASA, Arcugnano, Vicenza, Italy)	Peak powers: 3 kW	3000 J	Anteromedial and lateral surfaces of the knee with the knee flexed to 90° Posteromedial and lateral surfaces with the knee extended in prone position	Transverse and longitudinal scanning with hand piece being perpendicular to the treated area Anterior or posterior knee surface scanned in two subphases (initial and final) with three fluency levels	ET: range of motion, flexibility, stretching, strengthening exercises
Anna 2016	Semiconductive neodymium laser IV produced by BTL (wavelength 1064 nm)	Peak power: 12 W	3300J	First three procedures: medial and lateral sides of the knee Next 4 sessions: medial side of the knee	First three procedures: medial and lateral sides of the knee. distant application, 2 minutes, 25 Hz Next 4 sessions: medial side of the knee. Dose 120 J/cm^2, treated area 25 cm^2, 10min (bio stimulating parameters)	PL: sham laser treatment, without turning on the light beam
Nazari 2018	Nd: YAG laser with wavelength of 1064 nm (Fysiomed, Belgium)	Peak power: 5 W	2400 J	The medial and lateral sides of the knee with the patient in a supine position and the knee flexed at 30°	A slow manual scanning in longitudinal and perpendicular direction with a 6-cm probe placed vertically in contact with the joint line	CPT: TENS and US ET: muscle strengthening, flexibility
Kheshie 2014	Pulsed Nd: YAG laser, produced by HIRO 3 device (ASA, Arcugnano, Vicenza, Italy)	Peak powers: 3 kW	1250 J	Anterior, medial, and lateral aspects of the knee joint in supine lying position with the knee flexed at 30°	The scanning performed transversely and longitudinally in the knee joint with emphasis on the application on the joint line between the tibial and femoral epicondyles	PL + EX group: PL, range of motion, muscle strengthening, flexibility exercises
Gworys 2012	Synchronized two-wave laser emitted by an MLS device and one-wave laser/808 nm, 905 nm	HILT 1: 400 mW, energy density 6.21 J/cm^2 nm HILT 2: 1100 mW, energy density 3.28 J/cm^2	HILT 1: 148.8 J HILT 2: 79.2 J	Three points: medial and lateral of the knee joint gap Two points: superior and inferior aspect of the patellofemoral joint Two points: popliteal fossa	Laser energy administered as contact, single- point, slight pressure irradiation with the use of a laser probe with a lens applicator	PL simulated without actual irradiation
Kim 2016	HILT device (HEALTRON, United Technology Inc., Israel)	No details	No details	Tibia and femoral epicondyle with patient's knee bent at around 30°	Keep a separation distance of around 1 cm between the handpiece and the skin throughout the treatment	CPT: hot pack treatment, ultrasonic waves
Mazlum 2020	Nd: YAG Laser (BTL-6000)	Peak powers: 12 kW	300 J	No details	No details	PL + ET: PL + range of motion, stretching, strengthening, flexibility
Mostafa 2022	Nd: YAG laser therapy through the HIRO 03 device (ASA, Arcugnano, Vicenza, Italy) with wavelength of 1064 nm	Peak powers: 3 kW	18 J	The medial side of the knee while the patient lay supine with the knee exed at 30 degree	The HILT handpiece moved transversely and longitudinally in the anterior, medial, and lateral aspects of the knee joint, emphasizing the joint line between the tibial and femoral epicondyles	Extracorporeal shock wave therapy
Samaan 2022	Nd:YAG Laser (BTL-6000 High Intensity Laser 12 W) with wavelength of 1064 nm	Peak powers: 12 kW	300 J (the analgesic mode) 3000 J (the biostimulation mode)	Both side of the knee	All treatments standardized using a device that placed the participant in a supine position and the semi knee flexion 90°	CPT: low-intensity pulsed ultrasound, active ROM exercises, muscle strengthening, and flexibility exercises

ET: exercise therapies; PL: placebo laser therapies; CPT: conventional therapies.

Table 4
Methodological quality of included studies

Study ID	Items of PEDro scale											Total	Level
	1	2	3	4	5	6	7	8	9	10	11		
Alayat 2017	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	7/10	Good
Anna 2016	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	6/10	Good
Nazari 2019	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	6/10	Good
Kheshie 2014	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	6/10	Good
Gworys 2012	Yes	Yes	No	No	No	No	No	Yes	Yes	No	Yes	4/10	Poor
Kim 2016	Yes	Yes	No	No	No	No	No	Yes	Yes	Yes	Yes	5/10	Fair
Mazlum 2020	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	9/10	Excellent
Mostafa 2022	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	8/10	Good
Samaan 2022	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8/10	Good

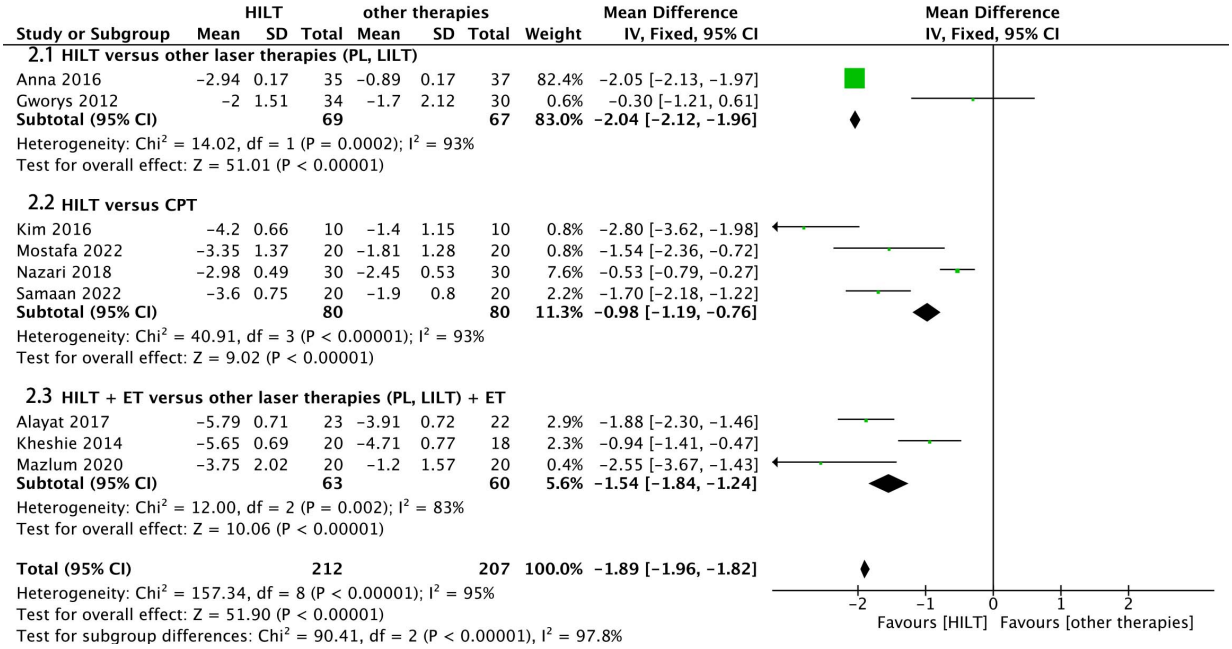

Fig. 2. Forest plot of knee pain VAS scores for HILT versus other therapies.

of HILT and PL in the treatment of KOA pain. A total of 133 subjects in these two studies used VAS to evaluate changes in pain before and after treatment. One study performed by Gworys and colleagues [48] investigated the effectiveness of HILT (dose 12.4 J/point) in contrast to PL therapy on relieving knee pain in patients with KOA, showing that the largest improvement of pain relief was seen in the HILT group after 10 sessions of treatment. In another study, Anna et al. [44] demonstrated that HILT was capable of producing statistically significant immediate (7 days), cumulative, and long lasting (three months) effect on pain in KOA compared to LILT therapy.

The high-intensity laser used in Anna's research [44] had a wavelength of 1064 nm and an energy density of 12 J/cm^2 (first 3 sessions) and 120 J/cm^2 (last 4 sessions), while the high-intensity laser used in Gworys's study [48] had a wavelength of 810 nm and an energy density of 12.6 J/cm^2, a total of 10 sessions were treated. In addition, in Anna's study [44], the duration of symptoms in the included population was more than 4 years, while the duration of patients included in Gworys's study [48] was more than 6 weeks.

The meta-analysis demonstrated significant pain relief effects of HILT compared to other laser therapies (MD, -2.04, 95% CI, -2.12 to -1.96; $Z = 51.01$, $P < 0.01$) (Fig. 2). In summary, those two studies [44,48] (136 people; one [44] with good quality, another [48] with poor quality) gave an indication that there was moderate evidence that HILT could be a promising new possibility in pain relief among patients with KOA compared with sham laser therapy in a short-term treatment.

Conflicting evidence showed that HILT and LILT had no significant difference in improving KOA pain.

3.5. HILT versus CPT

Four studies [26,45,47,49] (three [26,45,49] with good quality, one [47] with fair quality, 160 people in total) were performed to compare pain relieving effects between HILT and CPT (TENS, Ultrasound, ESWT), showing that HILT was significantly more effective than CPT in decreasing the VAS score after 10 or 12 sessions of treatment, among which one study [45] also demonstrated a long-lasting effect (after 12 weeks) of HILT on pain relief. The populations of the four studies were both 50–75 years old.

The type of high-intensity laser in Nazari's research [45] was Nd: YAG laser, the wavelength of 1064 nm, the frequency was 30 Hz, the peak power was 5 W, the energy density was 60 J/cm^2, and the total amount of each treatment was 2400 J. The type of HILT used by Samaan, and colleagues [26] was similar with that used by Nazari [45], but its maximum power was 12 kw. The bio-stimulation and analgesic modes were applied. The analgesic mode was applied on the first 3 days with a total of 300 J applied as 12 J/m^2 25 cm^2 at a frequency of 25 Hz in these sessions. The bio-stimulation mode was implemented as of the fourth session with a total of 3000 J applied as 120 J/cm^2 in this mode. The type of high-intensity laser in Kim's research [47] was HEALTRON (United Technology Inc., Israel), the frequency was 15 Hz, and the energy density was 1500 mJ/cm^2, and the total treatment volume was not described. Participants in Mostafa's [49] study received high-intensity pulsed Nd:YAG laser therapy through the HIRO 03 device (ASA, Arcugnano, Vicenza, Italy) at a frequency of 30 Hz and total delivered energy of 1500 mJ/cm^2 in each session, three sessions/week for 4 weeks.

The meta-analysis demonstrated significant pain relief effects of HILT compared to CPT (MD, -0.98, 95% CI, -1.19 to -0.76; $Z = 9.02$, $P < 0.01$) (Fig. 2). In summary, there is strong evidence that HILT for patients with KOA could be an effective modality on treating pain compared to CPT.

3.6. HILT + ET versus other laser therapies (PL, LILT) + ET

Three studies [25,43,46] compared HILT + ET versus PL + ET (123 people in total). In Kheshie's [46] and Mazlum's studies [25], the duration of the patient's disease was more than 6 months, while in the study of Alayat et al. [43], the duration of the patient's pain was more than 3 months. Alayat et al. [43] demonstrated that HILT + ET was more effective than PL + ET in the treatment of KOA pain after 6 weeks treatment and 3 months of follow-up. Similarly, Kheshie and colleagues [46] showed that HILT combined with ET was more effective than LLLT combined with ET, and both protocols were better than PL + ET in relieving patients' pain after 6 weeks. Mazlum's [25] study compared the effects of HILT + ET versus PL + ET on pain in patients with KOA and found that VAS score was significantly lower in the 6th week in HILT + ET group compared to the PL + ET group ($p < 0.05$).

Alayat [43] used Pulsed Nd:YAG laser therapy, wavelength (1064 nm), very high peak powers (3 kW), average power (10.5 W), high levels of fluency (510–1780 mJ/cm^2), pulse duration < 120 μs, low frequency (10–30 Hz), the total treatment volume is 3000 J/per treatment session, a total of 12 treatment sessions. The type of high-intensity laser used by Kheshie [46] was also Pulsed Nd:YAG laser therapy, with a treatment volume of 1250 J per session, and a total of 12 treatment sessions. Mazlum [25] also used 1064 nm wavelength Nd:YAG Laser (BTL-6000 High Intensity Laser 12 W), and its maximum output power was 12 W. The bio-stimulation and analgesic modes were used in the study. A total of 3000 J was applied as 120 J/cm^2 in this mode. A total of ten sessions were implemented.

The meta-analysis demonstrated a significant pain relief effect of HILT + ET versus PL + ET (MD, -1.54, 95% CI, -1.84 to -1.24; $Z = 10.06$, $P < 0.01$) (Fig. 2). Therefore, strong evidence showed that HILT combined with ET is more effective than PL combined with ET in alleviating pain in patients with KOA. Moderate evidence shows that HILT combined with ET is more effective than LILT combined with ET in alleviating pain in patients with KOA.

4. Discussion

These nine studies [25,26,43–49] all compared the effects of HILT and other treatments in relieving KOA pain. All studies have shown that HILT was effective in relieving KOA pain, and HILT is not inferior to other treatments in relieving knee pain, including LILT, ET, TENS, ultrasound therapy.

Biologically, KOA is commonly involved not only in the cartilage, subchondral bone, synovial tissue, but also pathoanatomic changes, including insufficient synthesizing extracellular matrix and collagen fibrils of chondrocytes [2,50]. Therefore, therapies with deeper

penetration may be needed to relieve pain in KOA patients.

The biological effects of laser therapies on human tissues may be related to the following main effects: thermal effects (increasing the temperature of the liquid, resulting in changes in intracellular pressure); mechanical effects (cellular mechanical pressure and kinetic changes); electrical effects (causing molecular structure changes of cell membranes and permeability); photochemistry (stimulation of photochemical reactions and selective absorption of certain chemicals in cells); biostimulation (providing quantum energy to cells without histological changes) [51]. According to the available evidence [25,26,29,31,43–49], the photodynamic and thermodynamics of HILT were the main reasons for the analgesic, anti-edema, anti-inflammatory and repairing effects of HILT. The thermal, photochemical, and mechanical effects of HILT were more obvious than other laser therapies [52]. The main advantage of HILT compared to LILT in pain-relieving effects is that as the power increases, the penetration depth increased (up to 100 mm) and thus worked better in deep structures such as the incomplete cartilage surface inside the knee joint [27,28,34,43,53]. The stimulation of nerve fiber regeneration by HILT also modulated the "gate control system" to achieve analgesic results [52]. HILT can also block cyclooxygenase and lipoxygenase as well as affect prostaglandins and the synthesis of prostacyclin used to regulate the components of the inflammatory response, exudation, alteration, and proliferation, and to stimulate the body's re-adaptation response to achieve anti-inflammatory purposes [44]. The effectiveness of HILT is based on laser pulses with a certain frequency and pulse width. Because of this high peak power, a large amount of energy can be delivered in a short period of time, whereas conventional laser treatments that deliver the same amount of energy take longer and work more slowly.

Conventional physical therapies, including TENS [45,47] (low-frequency electrical stimulation increasing pain threshold), Ultrasound [45] (mechanical stimulation, heat, and cellular massage effects), ESWT [49] (mechanical stimulation promoting subchondral bone repair and increasing the anoxic pain threshold) penetrates less deeply than HILT. However, HILT incorporates all the features of these modalities. When HILT is combined with ET, its pain relief effect may be better. On the one hand, the anti-inflammatory effect induced by HILT probably prompt compliance of exercises and increasing of exercises intensity, and on the other hand, exercise training improving the mechanical load shifts from the joint to the muscle compartments by increasing muscle strength [25,46]. Through this transfer of mechanics, cartilage regeneration increases, thus the thickness of the cartilage also increases [46], which potentially explains why this combination treatment is superior to other treatments. In a recent meta-analysis, Ahmad et al. [54] investigated that both LILT and HILT are beneficial as adjuncts to ET in the management of KOA pain. However, this meta-analysis did not compare the pain relief effect between HILT + ET and LILT + ET in individuals with KOA. Similar with our findings, Song et al. [34] and Wyszyńska et al. [55] investigated that the effectiveness of HILT on pain, stiffness, and function in patients with KOA is promising. However, these studies did not discuss intervention methods for the control group separately, which could lead to potential bias.

In addition, due to potential bias in the included populations (vary grades of KOA, different duration of onset), intervention methods (different types of HILTs, operating methods, and sites of action) in the included studies, the meta-analysis was highly heterogeneous (heterogeneity greater than 90%). Based on the quality level of the included studies, we also performed qualitative analyses to determine the level of evidence for the three subgroup comparisons.

5. Conclusion

HILT could be a promising modality in alleviating KOA pain, especially when it was implemented in combination with ET. HILT should be recommended for pain relief in patients with KOA over other treatments.

This review limits the age of the eligible population to 45 years and older and does not consider the effect of high-intensity laser on traumatic KOA pain. Due to the limited number of included articles, the current study only provided a qualitative description without conducting a meta-analysis of the effect after follow-up. Therefore, future meta-analysis can consider the use of hierarchical analysis to study the effect of HILT on the pain relief effects of traumatic KOA and explore the long effect of HILT.

Ethical approval

Not applicable.

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Informed consent

Not applicable.

Conflict of interest

None to report.

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Author contributions

PC was responsible for the drafting, revising and literature search of the paper. XW registered the paper. WW was responsible for literature search and data extraction. CC was responsible for data extraction of the included studies. HL identified the overall framework and provided statistical support.

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