Osteoarthritis and Cartilage 23 (2015) 1437–1444

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Review

Effectiveness of low-level laser therapy in patients with knee osteoarthritis: a systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 5 January 2015
Accepted 2 April 2015

Keywords:
Knee osteoarthritis
Low-level laser therapy
Pain
WOMAC

SUMMARY

Objective: To investigate the efficacy of low-level laser therapy (LLLT) treatment of knee osteoarthritis (KOA) by a systematic literature search with meta-analyses on selected studies.
Design: MEDLINE, EMBASE, ISI Web of Science and Cochrane Library were systematically searched from January 2000 to November 2014. Included studies were randomized controlled trials (RCTs) written in English that compared LLLT (at least eight treatment sessions) with sham laser in KOA patients. The efficacy effective size was estimated by the standardized mean difference (SMD). Standard fixed or random-effects meta-analysis was used, and inconsistency was evaluated by the I-squared index (I^2).
Results: Of 612 studies, nine RCTs (seven double-blind, two single-blind, totaling 518 patients) met the criteria for inclusion. Based on seven studies, the SMD in visual analog scale (VAS) pain score right after therapy (RAT) (within 2 weeks after the therapy) was not significantly different between LLLT and control (SMD = −0.28 [95% CI = −0.66, 0.10], I^2 = 66%). No significant difference was identified in studies conforming to the World Association of Laser Therapy (WALT) recommendations (four studies) or on the basis of OA severity. There was no significant difference in the delayed response (12 weeks after end of therapy) between LLLT and control in VAS pain (five studies). Similarly, there was no evidence of LLLT effectiveness based on Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain, stiffness or function outcomes (five and three studies had outcome data right after and 12 weeks after therapy respectively).
Conclusion: Our findings indicate that the best available current evidence does not support the effectiveness of LLLT as a therapy for patients with KOA.

Introduction

There are still no disease-modifying treatments for knee osteoarthritis (KOA). The currently available options include palliative pharmacological and non-pharmacological modalities. The core goal of these treatments is to relieve joint pain, improve joint function and gain a better quality of life. Though nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to treat these patients, their high incidence of side effects, especially of the upper gastrointestinal tract, has limited their use[1]. Thus, many physical therapy agents such as ultrasound[2], electrical stimulation[3], strengthening exercise[4] and thermal therapy[5] have been introduced.

Because of its non-invasiveness and advantage of inciting nearly no adverse side effects, low-level laser therapy (LLLT) has

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http://dx.doi.org/10.1016/j.joca.2015.04.005
1063-4584/

been widely used to relieve pain in different musculoskeletal disorders[6,7]. It has been considered a promising therapeutic intervention, mainly because of its stimulatory effects on tissue metabolism and ability to modulate the inflammatory process after injury. Some reported effects include improved cellular oxygenation, release of neurotransmitter associated with pain modulation and release of anti-inflammatory, endogenous mediators[8]. Nonetheless, reported clinical therapeutic outcomes are conflicting. Studies are similarly conflicting regarding its usage in patients with KOA[9,10].

Recently there has been an increased number of randomized controlled trials (RCTs) assessing the effectiveness of LLLT in patients with KOA; they have not yet been integrated into a systematic review or meta-analysis. Therefore, the aim of this study was to evaluate, through a systematic review and meta-analysis, the effectiveness of LLLT on symptoms and function in patients with KOA.

Method

Search strategy and study selection

The following bibliographic databases were searched up to 11th November 2014: Medline *via* PubMed from 2000, EMBASE *via* OVID from 2000, Web of Science from 2000 as well as the Cochrane Central Register of Controlled Trials. The search strategy was: (Osteoarthritis OR osteoarthros*) AND (knee) AND (low-level laser therapy OR low intensity laser therapy OR low energy laser therapy OR LLLT OR LILT OR LELT OR infrared laser OR IR laser OR diode laser).

Two reviewers independently identified titles and abstracts relevant to applying LLLT to patients suffering from KOA. Full texts of the published articles, unpublished articles as well as unpublished data of completely finished and analyzed studies were included. The reference list of the full-text articles was also reviewed. To be included in this analysis, studies had to meet the following criteria: (1) be RCTs; (2) involve patients with KOA (as assessed with radiography or according to the American College of Rheumatology guidelines); (3) compare LLLT and placebo laser; (4) report pain and/or function outcomes of patients; (5) attain a PEDro score[11] of >5; and (6) be written in English. Trials with an unbalanced additional modality (e.g., education or exercise) between groups were excluded.

Quality assessment

Two independent reviewers assessed study quality or risk of bias in each study using the PEDro scale[11]. The 11-point PEDro scale has been accepted as a reliable[12] and valid[13] assessment tool and is the one most often employed for physical treatments. Briefly, a study with a score of ≥7 is considered to be of high methodological quality, while a study with a score of ≤5 is considered to be of low methodological quality. The methodological assessment was conducted by two independent reviewers and results compared. Discrepancies between the two independent reviewers were resolved by consensus after discussion, and a third reviewer was consulted if necessary.

Data extraction

Study data were extracted by two reviewers and checked for accuracy by a third reviewer including the intervention description, inclusion/exclusion criteria, baseline data, values for all outcomes at baseline, post-intervention and later follow-up (12 weeks). The primary outcomes of interest were the visual analog scale (VAS) pain scores (right after the intervention meaning within 2 weeks after the final therapy session), expressed in millimeters, and the Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores (pain, stiffness, function and total; right after the intervention). The secondary outcomes of interest were range of motion (ROM) right after therapy (RAT), and VAS pain and WOMAC scores (pain, stiffness and function) at or near 12 weeks after therapy. If the data were not presented in the study as mean and standard deviation, or were presented in a form that prevented calculation of mean and standard deviation, the original authors were contacted.

Statistical analysis

We performed the meta-analysis in conformance with the Cochrane Collaboration and the Quality of Reporting of Meta-analysis guidelines. Because all the primary and secondary outcomes were continuous outcome data, means and standard deviations were used to calculate a standard mean difference (SMD) and 95% confidence interval (CI) in the meta-analysis. We checked all results for clinical and statistical heterogeneity. Clinical heterogeneity, determined by Chi-squared test, was evaluated based on the study baseline, interventions, definition of outcome measures, concomitant treatment and follow-up. A P value <0.05 was considered significantly different. I^2 values were used for the evaluation of statistical heterogeneity (I^2-of 50% or more indicating presence of heterogeneity)[14,15]. We used a standard random-effects meta-analysis for the main analyses. Results right after therapy refer to the comparison of LLLT and placebo after the series of therapy sessions raging from 8 to 20 over 2–6 weeks. Results after 12 weeks of therapy refer to the evaluation of a delayed or maintained response approximately 12 weeks after the last treatment session. A fixed-effects model was applied for the purpose of sensitivity analysis. Data were presented as a forest plot. We analyzed the effect of LLLT in subgroups distinguished by adherence to World Association of Laser Therapy (WALT) guidelines[16,17] and KOA severity[18]. Analyses were conducted using Review Manager Version 5.3 for MAC (The Nordic Cochrane Centre, The Cochrane Collaboration).

Results

Study selection and characteristics

Figure 1 illustrates the selection process for including studies in this meta-analysis. In total, 612 potential studies were found. Based on the title and abstract content, 595 of these studies were excluded. The full texts of the remaining 17 studies were read, and a further eight studies were excluded, resulting in nine studies[19–27] retained in the qualitative and quantitative synthesis of this review. A total of 518 patients were included: 264 patients in the LLLT group and 254 patients in the placebo group. In keeping with the WALT recommendations[16,17], each of these studies provided at least eight therapy sessions (range 8–20) over the course of 2–6 weeks. The characteristics of the included studies are listed in Tables I and II. Each of these studies included a placebo laser arm consisting of sham laser. The methodological quality assessment (Supplemental Table 1) showed that all these nine studies were of high quality (PEDro score of ≥7). All outcomes with appropriately reported data were extracted and included in the meta-analysis. Outcome measures were grouped according to their construct and design (Tables III and IV).

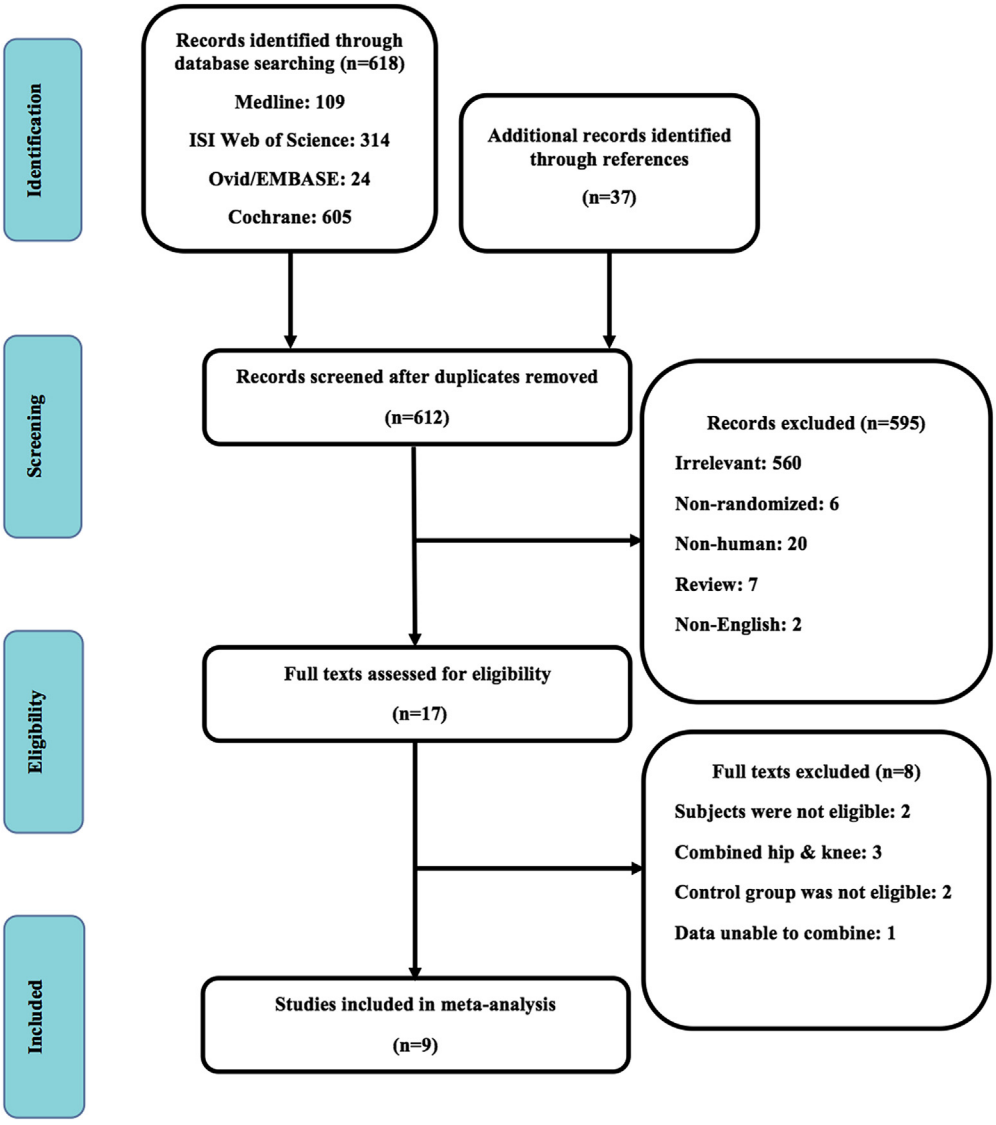

Fig. 1. CONSORT diagram showing screening process and search results.

Meta-analysis

Pain relief

Right after therapy, LLLT was not superior to placebo whether assessed by the VAS pain scale (SMD = −0.28 [95% CI = −0.66, 0.10], I^2 = 66%) (Fig. 2) or by WOMAC pain score (SMD = −0.25 [95% CI = −0.88, 0.37], I^2 = 79%) (Fig. 3). Subgroup analysis based on whether the studies were performed according to the WALT recommendations showed no significant difference between the two interventions in terms of VAS or WOMAC pain score right after therapy (Figs. 2 and 3). Moreover, another subgroup analysis based on the severity of OA (inclusion of patients with Kellgren–Lawrence grade IV KOA) also did not identify any significant differences between LLLT and placebo treatment (Supplemental Figs. 1 and 2). Analysis of the pooled data from week 12 after therapy also did not support the superiority of LLLT over placebo at this timepoint based on VAS pain (five pooled studies yielded SMD = −0.06 [95% CI = −0.30, 0.18], I^2 = 44%) (Table V) and WOMAC pain score (three pooled studies yielded SMD = 0.01, [95% CI = −0.27, 0.29], I^2 = 29%) (Table V).

WOMAC stiffness score

Five[19,21,25–27] (Table IV) of the included studies provided data on WOMAC stiffness score right after therapy. The meta-analysis showed no significant difference between the two groups (SMD = −0.07 [95% CI = −0.35, 0.21], I^2 = 48%) (Supplemental Fig. 3). The WOMAC stiffness score at week 12 after therapy was mentioned in only two studies[20,27] (Table IV); these pooled studies failed to identify a significant difference between the two treatment groups (SMD = 0.17 [95% CI = −0.24, 0.58], I^2 = 31%) (Table V).

WOMAC function score

Data on the WOMAC function score right after therapy were available in five studies[19,20,25–27]; data on the WOMAC function score at week 12 after therapy were available in three studies[20,24,27] (Table IV). The combined results showed no significant difference between LLLT and placebo groups at either timepoint (SMD = −0.40 [95% CI = −1.23, 0.43], I^2 = 88% (Supplemental Fig. 5); SMD = −0.10 [95% CI = −0.33, 0.53], I^2 = 53% (Table V)).

Table I
General information of recruited studies

Study	Type of studies	No.					Clinical baseline		PEDro score	WALT Recommendations
		Sample Size	Age (y)	Gender (M/F)	BMI	Dropouts	Pain	Function		
Gur *et al.*, 2003	DB-RCT	LLLT Group ($n = 30$)	58.64 (5.92)	5/25	31.17 (3.77)	0	73.2 (23.7)	54.56 (13.37)	9	N*
		Placebo Group ($n = 30$)	60.52 (6.91)	6/24	30.27 (3.11)	0	67.4 (17.3)	50.76 (15.42)		
Tascioglu *et al.*, 2004	DB-RCT	LLLT Group ($n = 20$)	62.86 (7.32)	6/14	27.56 (5.65)	0	68.0 (15.45)	36.60 (7.09)	9	Y†
		Placebo Group ($n = 20$)	64.27 (10.55)	7/13	29.56 (9.54)	0	63.88 (16.07)	39.46 (12.56)		
Yurtkuran *et al.*, 2007	DB-RCT	LLLT Group ($n = 28$)	51.83 (6.83)	1/27	31.76 (8.81)	1	64.7 (16.1)	47.53 (12.85)	9	N*
		Placebo Group ($n = 27$)	53.478 (7.13)	1/26	32.72 (3.71)	2	60.6 (21.7)	35.31 (13.75)		
Alfredo *et al.*, 2011	DB-RCT	LLLT Group ($n = 24$)	61.15 (7.52)	5/15	30.16 (4.12)	4	53.2 (35.5)	33.85 (16.93)	8	Y†
		Placebo Group ($n = 22$)	62.25 (6.87)	4/16	29.21 (4.95)	2	35.4 (30.6)	27.15 (11.32)		
Fukuda *et al.*, 2011	DB-RCT	LLLT Group ($n = 25$)	63.0 (9.0)	5/20	30.0 (3.5)	0	61 (26)	/	9	Y†
		Placebo Group ($n = 22$)	63.0 (8.0)	8/14	28.7 (4.1)	0	61 (23)			
Alghadir *et al.*, 2014	SB-RCT	LLLT Group ($n = 20$)	55.2 (8.14)	10/10	32.34 (5.77)	0	74.5 (10.5)	25.95 (9.23)	8	Y†
		Placebo Group ($n = 20$)	57 (7.77)	12/8	33.09 (4.98)	0	75.5 (13.5)	30.7 (11.03)		
Kheshie *et al.*, 2014	SB-RCT	LLLT Group ($n = 20$)	56.56 (7.86)	20/0	28.62 (5.20)	2	76.8 (6.58)	30.44 (3.66)	7	N*
		Placebo Group ($n = 20$)	55.6 (11.02)	20/0	28.51 (3.35)	5	78.7 (3.51)	31.00 (3.42)		
Al Rashoud *et al.*, 2014	DB-RCT	LLLT Group ($n = 26$)	52 (9)	10/16	38.0 (5.6)	0	64 (19)	61 (44-71)	9	N*
		Placebo Group ($n = 23$)	56 (11)	8/15	37.1 (5.3)	0	59 (18)	60 (49-70)		
Hinman *et al.*, 2014	DB-RCT	LLLT Group ($n = 71$)	63.4(8.7)	43/28	30.7 (6.1)	13	49 (19)	27.0 (11.3)	8	N*
		Placebo Group ($n = 70$)	63.8 (7.5)	31/39	28.8 (5.4)	19	50 (21)	27.5 (12.4)		

DB-RCT: Double blind-randomized controlled trial; SB-RCT: Single blind-randomized controlled trial; BMI: Body mass index.
Mean (standard deviation) are provided above for age, BMI, pain and function.
* N: Not conforming to WALT recommendations.
† Y: Conforming to WALT recommendations.

Table II
Severity of OA in included studies

Studies	Group	Severity of OA		
		Grade II	Grade III	Grade IV
Gur *et al.*, 2003	LLLT Group	14	10	6
	Placebo Group	13	11	6
Tascioglu *et al.*, 2004	LLLT Group	12	8	0
	Placebo Group	11	9	0
Yurtkuran *et al.*, 2007	LLLT Group	Patients with Kellgren–Lawrence		
	Placebo Group	Grade II and III		
Alfredo *et al.*, 2011	LLLT Group	4	9	7
	Placebo Group	9	4	7
Fukuda *et al.*, 2011	LLLT Group	31	8	2
	Placebo Group	27	9	2
Alghadir *et al.*, 2014	LLLT Group	16	4	0
	Placebo Group	17	3	0
Kheshie *et al.*, 2014	LLLT Group	Not provided		
	Placebo Group			
Al Rashoud *et al.*, 2014	LLLT Group	13	5	0
	Placebo Group	14	4	0
Hinman *et al.*, 2014	LLLT Group	Not provided		
	Placebo Group			

ROM right after therapy

Pooled data of three studies[20,22,23] (Table IV) on ROM right after therapy demonstrated no statistical difference between the two groups (SMD = 0.35 [95% CI = −0.75, 1.45], $I^2 = 90\%$) (Table V).

Discussion

Pain is the most common reason for persons with chronic musculoskeletal disorders to seek medical assistance. LLLT was introduced to control symptoms in a non-invasive manner with nearly no adverse effects and at low cost. However, the outcomes of the experimental and clinical studies, including for KOA, are conflicting. In 1992, Stelian *et al.*[28] performed an RCT to compare red (wavelength 630 nm), infrared (wavelength 830 nm) and placebo laser light emitters in patients with KOA. They observed significant functional improvement and pain reduction in the red and infrared groups but not in the placebo group. Soon, several additional studies were undertaken to evaluate the effectiveness of LLLT in KOA patients. In a double blind placebo controlled study, Bulow *et al.*[29] found there was no significant difference between LLLT and placebo treated groups for any outcome measures related to pain, strength or joint activity. Subsequently, Tascioglu *et al.*[26] also failed to observe any advantages of LLLT. These studies cast doubt on the effectiveness of LLLT in KOA patients. Recently, several high-quality RCTs have emerged in this field. Since no study has synthesized the results in a meta-analysis, we performed the current analysis, including nine studies with 518 patients. The meta-analysis showed no therapeutic benefit of LLLT compared with placebo for KOA patients with respect to pain relief or functional improvement, including right after therapy or at week 12 after therapy.

Potential mechanisms of pain reduction by laser therapy are still unknown. Several experimental studies suggest that LLLT has anti-inflammatory and/or analgesic effects. Some posit that LLLT could inhibit nociceptive signals at peripheral nerves[30]. Others believe LLLT could increase oxygenation of the tissue, thus alleviating and removing swelling, which could result in reduced pain[21]. Certain studies[31,32] reported enhanced joint cartilage regeneration after LLLT. However, the results of the interaction of laser light with the tissue depend on several factors such as the energy density, wavelength, output, number and timing of treatment sessions as well as the optical properties of the tissue.

Several studies using LLLT for musculoskeletal pain have shown that the greatest laser photobiomodulation effectiveness appears to

Table III
Technical features of laser use in the included for meta-analysis

Studies	Laser type	Laser model (manufacture)	Treatment time/No. of total sessions/No. of sessions per week	Laser continuous output (average pulse)	Energy density (J/cm^2)	Energy per point (J/point per session)
Gur *et al.*, 2003	Ga–As 904 nm	Frank Line IR 30	5 min/10/5	10 mW	3	3
Tascioglu *et al.*, 2004	Gal–Al–As 830 nm	Endolaser 476	120 s/20/5	50 mW	0.76	0.6
Yurtkuran *et al.*, 2007	Ga–As 904 nm	Roland Serie	120 s/10/5	4 mW	1.2	0.48
Alfredo *et al.*, 2011	Ga–As 904 nm	Irradia Class 3B	50 s/9/3	60 mW	6	3
Fukuda *et al.*, 2011	Ga–As 904 nm	Irradia Class 3B	50 s/9/3	60 mW	6	3
Alghadir *et al.*, 2014	Ga–As 850 nm	Intellect	60 s/8/2	100 mW	48	6
Kheshie *et al.*, 2014	Ga–As 830 nm	BTL-5000	33 s/12/2	800 mW	50	NA
Al Rashoud *et al.*, 2014	Ga–As 830 nm	Endolaser 476	40 s/9/3	30 mW	4	1.2
Hinman *et al.*, 2014	NA	Standard Class 3B	20 min/8/2	10 mW	NA	0.2

Abbreviation: NA, not available; min, minute; s, second.

Table IV
Description of outcome measures used in the studies included in the meta-analysis

Studies	Outcome measures		
	Pain	Stiffness	Function
Gur *et al.*, 2003	1. VAS pain (RAT, eighth, twelfth week) 2. Painless walking duration (min) (RAT, eighth, twelfth week) 3. Painless walking distance (m) (RAT, eighth, twelfth week)	1. Morning stiffness (min) (RAT, eighth, twelfth week)	1. ROM (RAT, eighth, twelfth week)
Tascioglu *et al.*, 2004	1. VAS pain (RAT, sixth month) 2. WOMAC pain (RAT, sixth month)	1. WOMAC stiffness (RAT, sixth month)	1. WOMAC function (RAT, sixth month)
Yurtkuran *et al.*, 2007	1. VAS pain (RAT, twelfth week) 2. WOMAC pain (RAT, twelfth week)	1. WOMAC stiffness (RAT, twelfth month)	1. WOMAC function (RAT, twelfth week)
Alfredo *et al.*, 2011	1. VAS pain (RAT, eleventh week) 2. WOMAC pain (RAT, eleventh week)	1.WOMAC Stiffness (RAT, eleventh week)	1. ROM (RAT, eleventh week) 2. WOMAC Function (RAT, eleventh week)
Fukuda *et al.*, 2011	1. VAS pain (RAT)	NA	1. ROM (RAT)
Alghadir *et al.*, 2014	1. VAS pain (RAT) 2. WOMAC pain (RAT)	1. WOMAC Stiffness (RAT)	1. WOMAC Function (RAT)
Kheshie *et al.*, 2014	1. WOMAC pain (RAT)	1. WOMAC Stiffness (RAT)	1. WOMAC Function (RAT)
Al Rashoud *et al.*, 2014	1. VAS pain (RAT, sixth week, sixth month)	NA	NA
Hinman *et al.*, 2014	1. VAS (twelfth week, 1 year) 2. WOMAC pain (twelfth week, 1 year)	NA	1. WOMAC function (twelfth week, 1 year)

NA: Not available.

be linked to higher irradiation protocols (energy density) as well as to a greater number of sessions and frequency of application. By comparing several previous clinical trials, Fukuda *et al.*[22] and Alghadir *et al.*[21] concluded that only applications of an LLLT energy density greater than 3 J/point could be effective. According to the WALT[16,17] table of recommended doses, the optimal energy density for KOA is supposed to be a minimum of 4 J per point. Five included studies[20–22,24,26] followed these WALT recommendations. Even pooling these four studies, we failed to observe a statistically significant difference of LLLT compared to placebo for VAS pain or WOMAC pain score right after therapy. The WALT guidelines recommend daily treatment for 2 weeks or treatment every other day for 3–4 weeks (totaling 6 to 12 sessions). All the included studies provided or exceeded the recommended session number.

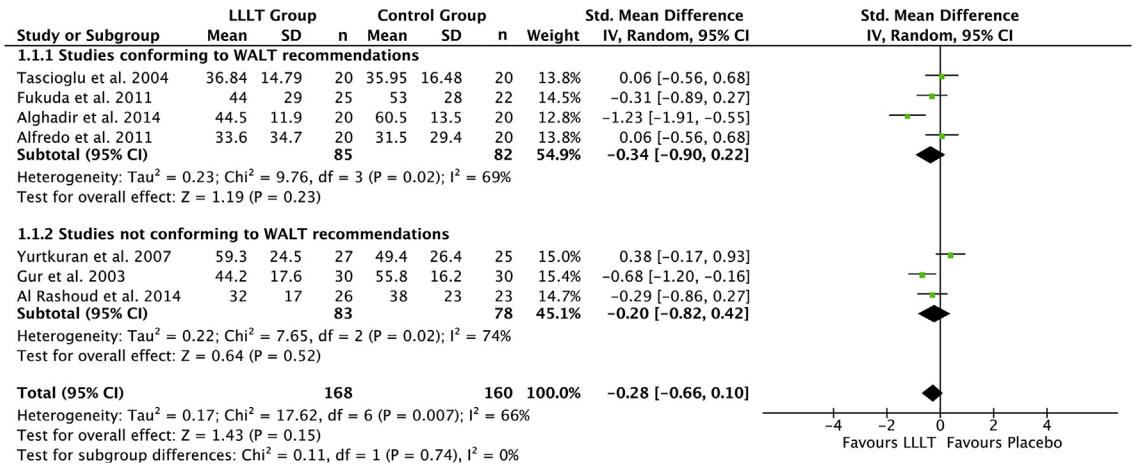

Fig. 2. Forest plot analysis of the VAS pain score right after therapy (subgroup analysis based on whether studies conformed to WALT recommendations or not).

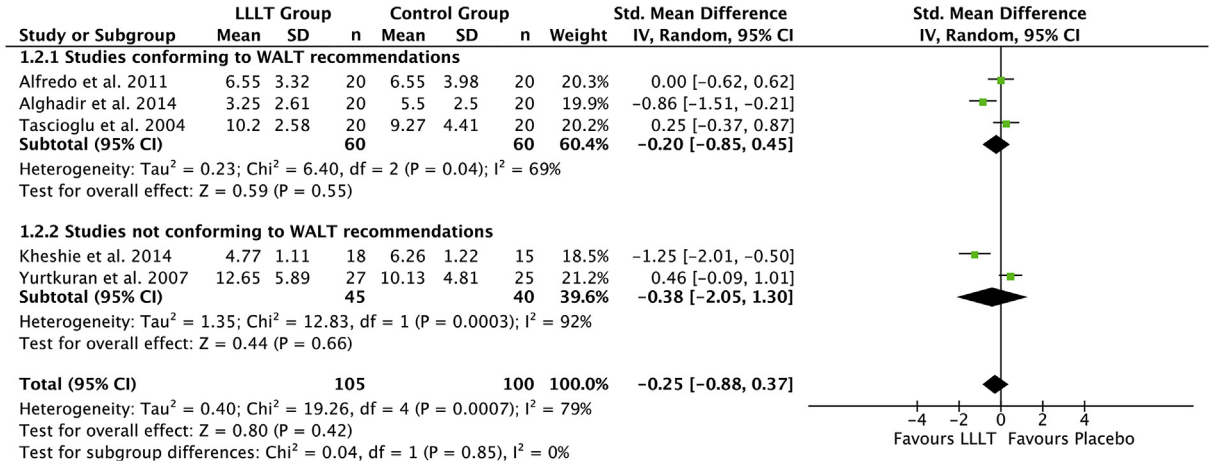

Fig. 3. Forest plot analysis of the WOMAC pain score right after therapy (subgroup analysis based on whether studies conformed to WALT recommendations or not).

Though Tascioglu *et al.*[26] provided the greatest number of sessions (20), they still did not observe a difference between LLLT over placebo.

Wavelength is also considered an essential parameter for beneficial outcomes of LLLT. Biophysically, it determines the ability of a laser to penetrate tissue. Light with a wavelength range of 700–1000 nm is infrared and invisible; its ability to penetrate tissue is better than the red wavelength, thus this range of wavelength is usually used in clinical treatment[33]. A clinical study of laser irradiation in skin flaps has shown that penetration increases linearly with wavelengths from 450 nm to 1030 nm[34]. Another study illustrated that a greater amount of energy penetrated rabbit skin with a wavelength of 904 nm than with a wavelength of 632.8 nm[35]. Thus, the WALT guidelines recommend wavelengths of 780 nm–860 nm[16] or 904 nm[17] for LLLT in KOA patients. All the included studies used a wavelength within this recommended range.

Besides wavelength, optical properties of tissue are also believed to be vital to the treatment response to LLLT. The penetrability of certain wavelengths varies in different tissues. According to Joensen *et al.*[36], the amount of penetrating light energy is 20% for a wavelength of 810 nm and 58% for a wavelength of 904 nm. King *et al.*[37] found that the penetration of laser irradiation into skin is limited to a few millimeters. This might explain why some studies failed to find LLLT effective for large joints while the results for small joints seem promising[37].

The severity of the disease is considered a typical host factor that might affect treatment outcomes[38]. In a study assessing the efficacy of LLLT for temporomandibular joint arthritis, Conti *et al.*[39] reported a better outcome in the less severe group. However, up to now there has been no such study of KOA patients. In this meta-analysis, we performed a subgroup analysis based on whether the included study enrolled patients with Kellgren–Lawrence grade IV KOA. The results did not favor the superiority of LLLT in either the less or more severely affected subgroups.

As can be seen here, variation in the effectiveness of LLLT in KOA patients could be related to a variety of factors. At present it is still difficult to determine the optimal dosage, treatment schedule, energy density, output and wavelength. This may explain why a high degree of heterogeneity was observed in several outcomes.

This review has both strengths and limitations. Strengths include selection of studies, all with high methodological quality based on the PEDro score. In combining studies with small samples, we provide the most evidence for effects of LLLT. Additionally, this meta-analysis was performed on the basis of the Cochrane Collaboration's principle[40] and designed to be rigorous in its search strategy. Some limitations of the current meta-analysis warrant discussion. First and foremost is the high degree of heterogeneity between the pooled studies. The random-effects model was chosen due to the presence of this heterogeneity. Second, several of the included studies used balanced quadriceps exercise as an additional treatment in both LLLT and placebo groups. Third, one study reported the continuous data such as VAS pain and WOMAC scores without SDs. Though we tried to contact the authors to get the information, the missing data could not be obtained; thus, these analyses in some cases did not have full data available.

Conclusion

The results of our systematic review and meta-analysis have provided the best current evidence on LLLT in the treatment of KOA. This study indicated that LLLT has neither early nor later benefits in reducing pain or improving function in patients with KOA.

Table V
Meta-analyses of Standard Mean Differences in various continuous parameters between the LLLT and placebo groups*

Parameters	No. of patients		Standard mean difference (95% CI)	*P* Value	I^2
	LLLT group (n)	Placebo group (n)			
ROM right after therapy	75	72	0.32 [−0.75, 1.45]	0.54	90%
VAS score at week 12 after therapy	135	126	−0.06 [−0.30, 0.18]	0.63	44%
WOMAC pain score at week 12 after therapy	105	96	0.01 [−0.27, 0.29]	0.95	29%
WOMAC stiffness score at week 12 after therapy	47	45	0.17 [−0.24, 0.58]	0.42	31%
WOMAC function score at week 12 after therapy	105	96	0.10 [−0.33, 0.53]	0.65	53%

* Heterogeneity was determined by Chi-squared test. I^2 value was used for the evaluation of statistical heterogeneity (I^2- of 50% or more indicating presence of heterogeneity). Randomized effects model was used when $I^2 \geq 50$, otherwise fixed-effects model was used.

Contributions

Drs ZeYu Huang, FuXing Pei and Virginia Byers Kraus take responsibility for the integrity of the work as a whole. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

Conception and design: ZeYu Huang, FuXing Pei, Virginia Byers Kraus.

Collection and assembly of data: ZeYu Huang, Jing Chen, Jun Ma.

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Role of the funding source

This research was funded by the China Health Ministry Program (201302007). We recognize the support of the China Scholarship Council (CSC). These organizations had no involvement in the study design, collection, analysis or interpretation of data, in the writing of the manuscript, or in the decision to submit the manuscript for publication.

Conflict of interest

None of the authors have competing interests to disclose. No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

Acknowledgments

We wish to acknowledge funding to support the effort of ZH by the China Health Ministry Program (201302007). We also wish to acknowledge support for the effort of VBK by National Institutes of Health/National Institute on Aging OAIC P30-AG-028716.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.joca.2015.04.005.

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