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Efficacy of low-level laser therapy on pain and disability in knee osteoarthritis: systematic review and meta-analysis of randomised placebo-controlled trials

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ABSTRACT

Objectives Low-level laser therapy (LLLT) is not recommended in major knee osteoarthritis (KOA) treatment guidelines. We investigated whether a LLLT dose–response relationship exists in KOA.

Design Systematic review and meta-analysis.

Data sources Eligible articles were identified through PubMed, Embase, Cumulative Index to Nursing and Allied Health Literature, Physiotherapy Evidence Database and Cochrane Central Register of Controlled Trials on 18 February 2019, reference lists, a book, citations and experts in the field.

Eligibility criteria for selecting studies We solely included randomised placebo-controlled trials involving participants with KOA according to the American College of Rheumatology and/or Kellgren/Lawrence criteria, in which LLLT was applied to participants' knee(s). There were no language restrictions.

Data extraction and synthesis The included trials were synthesised with random effects meta-analyses and subgrouped by dose using the World Association for Laser Therapy treatment recommendations. Cochrane's risk-of-bias tool was used.

Results 22 trials (n=1063) were meta-analysed. Risk of bias was insignificant. Overall, pain was significantly reduced by LLLT compared with placebo at the end of therapy (14.23 mm Visual Analogue Scale (VAS; 95% CI 7.31 to 21.14)) and during follow-ups 1–12 weeks later (15.92 mm VAS (95% CI 6.47 to 25.37)). The subgroup analysis revealed that pain was significantly reduced by the recommended LLLT doses compared with placebo at the end of therapy (18.71 mm (95% CI 9.42 to 27.99)) and during follow-ups 2–12 weeks after the end of therapy (23.23 mm VAS (95% CI 10.60 to 35.86)). The pain reduction from the recommended LLLT doses peaked during follow-ups 2–4 weeks after the end of therapy (31.87 mm VAS significantly beyond placebo (95% CI 18.18 to 45.56)). Disability was also statistically significantly reduced by LLLT. No adverse events were reported.

Conclusion LLLT reduces pain and disability in KOA at 4–8 J with 785–860 nm wavelength and at 1–3 J with 904 nm wavelength per treatment spot.

PROSPERO registration number CRD42016035587.

Strengths and limitations of this study

- The review was conducted in conformance with a detailed a priori published protocol, which included, for example, laser dose subgroup criteria.
- No language restrictions were applied; four (18%) of the included trials were reported in non-English language.
- A series of meta-analyses were conducted to estimate the effect of low-level laser therapy on pain over time.
- Three persons each independently extracted the outcome data from the included trial articles to ensure high reproducibility of the meta-analyses.
- The review lacks quality-of-life analyses, a detailed disability time-effect analysis and direct comparisons between low-level laser therapy and other interventions.

INTRODUCTION

Approximately 13% of women and 10% of men in the population aged ≥60 years suffer from knee osteoarthritis (KOA) in the USA.[1] KOA is a degenerative inflammatory disease affecting the entire joint and is characterised by progressive loss of cartilage and associated with pain, disability and reduced quality of life (QoL).[1] Increased inflammatory activity is associated with higher pain intensity and more rapid KOA disease progression.[1 2]

Some of the conservative intervention options for KOA are exercise therapy, non-steroidal anti-inflammatory drugs (NSAIDs) and anti-inflammatory low-level laser therapy (LLLT). There is evidence that exercise therapy reduces pain and disability and improves QoL in persons with KOA.[3 4] NSAIDs are recommended in most KOA clinical treatment guidelines and is probably the most frequently prescribed therapy category for osteoarthritis, despite intake of these

drugs is associated with negative side effects,[5] which is problematic, especially since the disease requires long-term treatment. Furthermore, a recently published network meta-analysis indicates that the pain relieving effect of NSAIDs in KOA beyond placebo is small to moderate (depending on drug type).[6] Likewise, in the first systematic review on this topic, the pain relieving effect of NSAIDs was estimated to be only 10.1 mm on the 0–100 mm Visual Analogue Scale (VAS) better than placebo.[7]

LLLT is a non-invasive treatment modality,[8 9] which has been reported to induce anti-inflammatory effects.[9–14] LLLT was compared with NSAID in rats with KOA by Tomazoni *et al* in a laboratory; NSAID (10 mg diclofenac/knee/session) and LLLT (830 nm wavelength, 6 J/knee/session) reduced similar levels of inflammatory cells and metalloproteinase (MP-3 and MP-13). In addition, LLLT reduced the expression of proinflammatory cytokines (interleukin-1β (IL-1β) and IL-6 and tumour necrosis factor α), myeloperoxidase and prostaglandin E_2 significantly more than NSAID did.[10 11]

LLLT has been applied to rabbits with KOA three times per week for 8 weeks in a placebo-controlled experiment by Wang *et al*.[12] At the end of treatment week 6, they found that LLLT had significantly reduced pain and synovitis and the production of IL-1β, inducible nitric oxide synthase and MP-3 and slowed down loss of metallopeptidase inhibitor 1. Two weeks later, LLLT had significantly reduced MP-1 and MP-13 and slowed down loss of collagen II, aggrecan and transforming growth factor beta, and the previous changes were sustained.[12] These findings indicate that the effects of LLLT increase over time.

Pallotta *et al*[14] conducted a study on LLLT in rats with acute knee inflammation, which demonstrated that even though LLLT (810 nm) significantly enhanced cyclooxygenase (COX-1 and COX-2) expression it significantly reduced several other inflammatory makers, that is, leucocyte infiltration, myeloperoxidase, IL-1 and IL-6 and especially prostaglandin E_2. Pallotta *et al*[14] hypothesised that the increase in COX levels by LLLT was involved in a production of inflammatory mediators related to the resolution of the inflammatory process.

LLLT is not recommended in major osteoarthritis treatment guidelines. LLLT for KOA was mentioned in the European League Against Rheumatism osteoarthritis guidelines (2018) but not recommended,[15] and in the Osteoarthritis Research Society International guidelines (2018), it was stressed that LLLT should not be considered a core intervention in the management of KOA.[16]

This may be partly due to conflicting results of two recently published systematic reviews on the current topic.[8 17] The conflicting results may arise from omission of relevant trials[8 17–23] and unresolved LLLT dose-related issues. Only Huang *et al*[17] conducted a LLLT dose–response relationship investigation in KOA, that is, by subgrouping the trials by laser dose, but they did not consider that World Association for Laser Therapy (WALT) recommends applying four times the laser dose with continuous irradiation compared to superpulsed irradiation.[22 24–26] Thus, it was unknown whether LLLT is effective in KOA, and we saw a need for a new systematic review.

The objectives of the current review were to estimate the effectiveness of LLLT in KOA regarding knee pain, disability and QoL, and we only considered placebo-controlled randomised clinical trials (RCTs) for inclusion to minimise risk of bias.

METHODS

This review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement 2009.[27]

Literature search and selection of studies

Any identified study was included if it was a placebo-controlled RCT involving participants with KOA according to the American College of Rheumatology tool and/or a radiographic inspection with the Kellgren/Lawrence (K/L) criteria, in which LLLT was applied to participants' knee(s) and self-reported pain, disability and/or QoL was reported. There were no language restrictions.

We updated a search for eligible articles indexed in PubMed, Embase, Cumulative Index to Nursing and Allied Health Literature, Physiotherapy Evidence Database and Cochrane Central Register of Controlled Trials on 18 February 2019. The database search strings contained synonyms for LLLT and KOA, and keywords were added when optional. The PubMed search string is available in the online supplementary material. The search was continued by reading reference lists of all the eligible trial and relevant review articles,[8 17 28] citations[29–33] and a laser book[34] and involving experts in the field.

Two reviewers (MBS and JMB) each independently selected the trial articles. Both reviewers scrutinised the titles/abstracts of all the publications identified in the search, and any accessible full-text article was retrieved if it was judged potential eligible by at least one reviewer. Both reviewers evaluated the full texts of all potentially eligible retrieved articles and made an independent decision to include or exclude each article, with close attention to the inclusion criteria. When selection disagreements could not be resolved by discussion, a third reviewer (IFN) made the final consensus-based decision. Any retrieved article not fulfilling the inclusion criteria was omitted and listed with reason for exclusion.

Risk-of-bias analysis

Two reviewers (MBS and JJ) each independently evaluated all included trials for risk of bias at the outcome level, using the Cochrane Collaboration's risk-of-bias tool.[35] When risk-of-bias disagreements could not be resolved by discussion, a third reviewer (IFN) made the final consensus-based decision. Likelihood of publication bias was assessed with graphical funnel plots.[35]

Data extraction and meta-analysis

Three reviewers (MBS, JMB and KVF) each independently extracted the data for meta-analysis. Two of the reviewers (MBS and KVF) each independently collected the other trial characteristics. The data-extraction forms were subsequently compared, and data disagreements were resolved by consensus-based discussions. Summary data were extracted, unless published individual participant data were available.[21] The results from the included trials for statistical analysis were selected from outcome scales in adherence to hierarchies published by Juhl *et al*.[36]

Pain intensity was the primary outcome. As pain reported with continuous, numeric and categorical/Likert scales highly correlates with pain measured using the VAS, the scores of all pain scales were transformed to 0%–100%, corresponding to 0–100 mm VAS.[37] The pain results were combined with the mean difference (MD) method, primarily using change scores, that is, when only final scores could be obtained from a trial, change and final scores were mixed in the analysis, since the MD method allows for this without introducing bias.[35]

Self-reported disability results were synthesised with the standardised mean difference (SMD) method using change scores solely. The SMD was adjusted to Hedges' *g* and interpreted as follows: SMDs of 0.2, ~0.5 and >0.8 represent a small, moderate and large effect, respectively.[35]

Lack of QoL data prohibited an analysis of this outcome.

Random effects meta-analyses were conducted, and impact from heterogeneity (inconsistency) on the analyses was examined using I^2 statistics. An I^2 value of 0% indicates no inconsistency, and an I^2 value of 100% indicates maximal inconsistency[35]; the values were categorised as low (25%), moderate (50%) and high (75%).[38]

SDs for analysis were extracted or estimated from other variance data in a prespecified prioritised order: (1) SD, (2) SE, (3) 95% CI, (4) p value, (5) IQR, (6) median of correlations, (7) visually from graph or (8) other methods.[35]

The trials were subgrouped by adherence and non-adherence to the WALT recommendations for laser dose per treatment spot, as prespecified. WALT recommends irradiating the knee joint line/synovia with the following doses per treatment spot: ≥4 J using 5–500 mW mean power 780–860 nm wavelength laser and/or ≥1 J using 5–500 mW mean power (>1000 mW peak power) 904 nm wavelength laser.[24 25]

The main meta-analyses were conducted using two prespecified time points of assessment, that is, immediately after the end of LLLT and last time point of assessment 1–12 weeks after the end of LLLT (follow-up).

MBS performed the meta-analyses, under supervision of JMB, using the software programme Excel 2016 (Microsoft) and Review Manager Version V.5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

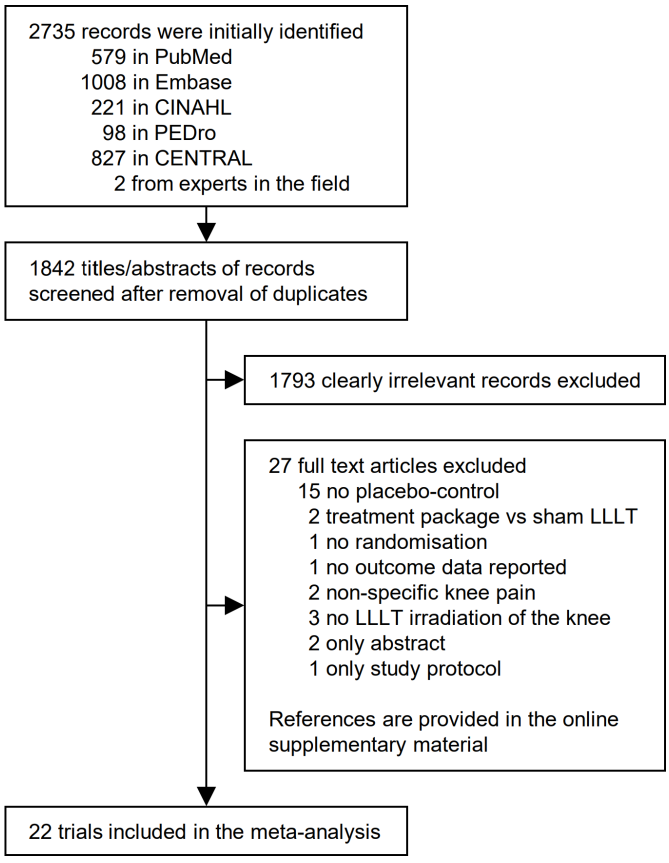

Figure 1 Flow chart illustrating the trial identification process. CENTRAL, Cochrane Central Register of Controlled Trials; CINAHL, Cumulative Index to Nursing and Allied Health Literature; LLLT, low-level laser therapy; PEDro, Physiotherapy Evidence Database.

Patient and public involvement

Patients or the public were not involved in the conceptualisation or carrying out of this research.

RESULTS

In total, 2735 records were identified in the search, of which 22 trial articles were judged eligible and included in the review (n=1089; figure 1 and tables 1–2) with data for meta-analysis (n=1063). Four included trials were not reported in the English language[19 21 23 39] and one included trial was unpublished (Gur and Oktayoglu). Excluded articles initially judged potentially eligible were listed with reasons for omission (online supplementary material).

At the group level, the mean age of the participants was 60.25 (50.11–69) years (data from 19 trials), the mean percentage of women was 69.63% (0–100%; data from 17 trials), the mean body mass index of the participants was 29.55 (25.8–38; data from 14 trials), the mean of median K/L grades was 2.37 (data from 13 trials) and the mean baseline pain was 63.61 mm VAS (35.25–92) (data from 22 trials). LLLT was used as an adjunct to exercise therapy in 11 trials. The mean duration of the treatment periods was 3.53 weeks with the recommended LLLT doses and 3.7

Table 1 Characteristics of the included trials

First author	Intervention group at baseline	Control group at baseline	Intervention versus control programme	Outcome scales, week of reassessment
Al Rashoud 2014[31]	N: 26 Women: 62% Age: 52 years BMI: 38 VAS pain: 64 mm K/L: -	N: 23 Women: 65% Age: 56 years BMI: 37.1 VAS pain: 59 mm K/L: -	3 weeks of exercise therapy, advice and LLLT versus 3 weeks of exercise therapy, advice and sham LLLT	Pain: VAS (movement) Disability: SKFS QoL: – Week of assessment: 2, **3**, **9**, 29
Alfredo 2011/2018[29 52]	N: 24 Women: 75% Age: 61.15 years BMI: 30.16 VAS pain: 53.2 mm K/L: 3	N: 22 Women: 80% Age: 62.25 years BMI: 29.21 VAS pain: 35.4 mm K/L: 2	3 weeks of LLLT followed by 8 weeks of exercise therapy versus 3 weeks of sham LLLT followed by 8 weeks of exercise therapy	Pain: WOMAC Disability: WOMAC QoL: – Week of assessment: **3**, **11**, 24, 37
Alghadir 2014[32]	N: 20 Women: 50% Age: 55.2 years BMI: 32.34 VAS pain: 74.5 mm K/L: 2	N: 20 Women: 40% Age: 57 years BMI: 33.09 VAS pain: 75.5 mm K/L: 2	4 weeks of exercise therapy, heat packs and LLLT versus 4 weeks of exercise therapy, heat packs and sham LLLT	Pain: WOMAC Disability: WOMAC QoL: – Week of assessment: **4**
Bagheri 2011[23]	N: 18 Women: 83.13% Age: 58.32 years BMI: 28.87 VAS pain: 67 mm K/L: –	N: 18 Women: 83.13% Age: 56.14 years BMI: 27.66 VAS pain: 59 mm K/L: –	2 weeks of exercise therapy, therapeutic ultrasound, TENS and LLLT versus 2 weeks of exercise therapy, therapeutic ultrasound, TENS and sham LLLT	Pain: WOMAC (VAS) 0–100 Disability: WOMAC QoL: – Week of assessment: **2**
Bülow 1994[20]	N: 14 Women: – Age: – BMI: – VAS pain: 65.08 mm K/L: –	N: 15 Women: – Age: – BMI: – VAS pain: 56.35 mm K/L: –	3 weeks of LLLT versus 3 weeks of sham LLLT	Pain: 0–121 Likert scale (movement/rest) Disability: – QoL: – Week of assessment: **3**, **6**
Delkhosh 2018[39]	N: 15 Women: 100% Age: 55.9 years BMI: 26.5 VAS pain: 57 mm K/L: –	N: 15 Women: 100% Age: 58.3 years BMI: 27.8 VAS pain: 45 mm K/L: –	2 weeks of exercise therapy, therapeutic ultrasound, TENS and LLLT versus 2 weeks of exercise therapy, therapeutic ultrasound, TENS and sham LLLT	Pain: VAS Disability: WOMAC QoL: – Week of assessment: **2**, **8**
Fukuda 2011[30]	N: 25 Women: 80% Age: 63 years BMI: 30 VAS pain: 61 mm K/L: 2	N: 22 Women: 64% Age: 63 years BMI: 30 VAS pain: 62 mm K/L: 2	3 weeks of LLLT versus 3 weeks of sham LLLT	Pain: VNSP (movement) Disability: Lequesne QoL: – Week of assessment: **3**
Gur 2003[33] (1.5 J)	N: 30 Women: 83.3% Age: 58.64 years BMI: 31.17 VAS pain: 73.2 mm K/L: 2	N: 30 Women: 80% Age: 60.52 years BMI: 30.27 VAS pain: 67.4 mm K/L: 2	14 weeks of exercise therapy and 2 weeks of LLLT versus 14 weeks of exercise therapy and 2 weeks of sham LLLT	Pain: VAS (movement) Disability: – QoL: – Week of assessment: 6, 10, **14**
Gur 2003[33] (1 J)	N: 30 Women: 76.7% Age: 59.8 years BMI: 28.49 VAS pain: 74.4 mm K/L: 2	N: 30 Women: 80% Age: 60.52 years BMI: 30.27 VAS pain: 67.4 mm K/L: 2	14 weeks of exercise therapy and 2 weeks of LLLT versus 14 weeks of exercise therapy and 2 weeks of sham LLLT	Pain: VAS (movement) Disability: – QoL: – Week of assessment: 6, 10, **14**
Gur and Oktayoglu	N: 40 Women: 75% Age: 58.2 years BMI: 29.11 VAS pain: 88 mm K/L: 3	N: 40 Women: 72.5% Age: 58.26 years BMI: 30.11 VAS pain: 92 mm K/L: 3	14 weeks of exercise therapy and 2 weeks of LLLT versus 14 weeks of exercise therapy and 2 weeks of sham LLLT	Pain: VAS (movement) Disability: – QoL: – Week of assessment: 6, 10, **14**

Continued

Table 1 Continued

First author	Intervention group at baseline	Control group at baseline	Intervention versus control programme	Outcome scales, week of reassessment
Gworys 2012[18]	N: 34 Women: – Age: 57.6 BMI: – VAS pain: 54 mm K/L: –	N: 31 Women: – Age: 67.7 BMI: – VAS pain: – K/L: –	2 weeks of LLLT versus 2 weeks of sham LLLT	Pain: VAS Disability: Lequesne QoL: – Week of assessment: **2**
Hegedűs 2009[53]	N: 18 Women: – Age: – BMI: – VAS pain: 57.5 mm K/L: 2	N: 17 Women: – Age: – BMI: – VAS pain: 56.2 mm K/L: 2	4 weeks of LLLT versus 4 weeks of sham LLLT	Pain: VAS Disability: – QoL: – Week of assessment: **4**, 6, **12**
Helianthi 2016[54]	N: 30 Women: 60% Age: 69 years BMI: 25.8 VAS pain: 60.2 mm K/L: 3	N: 29 Women: 82.8% Age: 68 years BMI: 26.3 VAS pain: 54.1 mm K/L: 3	5 weeks of LLLT versus 5 weeks of sham LLLT	Pain: VAS (movement) Disability: Lequesne QoL: – Week of assessment: 2, **5**, **7**
Hinman 2014[41]	N: 71 Women: 39% Age: 63.4 years BMI: 30.7 VAS pain: 41.5 mm K/L: –	N: 70 Women: 56% Age: 63.8 years BMI: 28.8 VAS pain: 43 mm K/L: –	12 weeks of LLLT versus 12 weeks of sham LLLT	Pain: WOMAC Disability: WOMAC QoL: AQoL-6D Week of assessment: **12**, 52
Jensen 1987[21]	N: 13 Women: – Age: – BMI: – VAS pain: 67 mm K/L: –	N: 16 Women: – Age: – BMI: – VAS pain: 72.6 mm K/L: –	1 week of LLLT versus 1 week of sham LLLT	Pain: 0–21 (movement) Disability: – QoL: – Week of assessment: **1**
Kheshie 2014[47]	N: 18 Women: 0% Age: 56.56 years BMI: 28.62 VAS pain: 76.8 mm K/L: 2.5	N: 15 Women: 0% Age: 55.6 years BMI: 28.51 VAS pain: 78.7 mm K/L: 2.5	6 weeks of exercise therapy and LLLT versus 6 weeks of exercise therapy and sham LLLT	Pain: WOMAC Disability: WOMAC QoL: – Week of assessment: **6**
Koutenaei 2017[55]	N: 20 Women: 85% Age: 52.3 years BMI: 28.4 VAS pain: 74 mm K/L: 3	N: 20 Women: 80% Age: 53 years BMI: 28.6 VAS pain: 65.5 mm K/L: 3	2 weeks of exercise therapy and LLLT versus 2 weeks of exercise therapy and sham LLLT	Pain: VAS (movement) Disability: – QoL: – Week of assessment: **2**, **4**
Mohammed 2018[56]	N: 20 Women: 85% Age: 55.25 years BMI:≥25 VAS pain: 70 mm K/L: 2	N: 20 Women: 85% Age: 50.11 years BMI:≥25 VAS pain: 80 mm K/L: 2	4 weeks of LLLT versus 4 weeks of sham LLLT	Pain: VAS Disability: – QoL: – Week of assessment: **4**
Nambi 2016[48]	N: 17 Women: – Age: 58 BMI: 26.9 VAS pain: 78 mm K/L: 3.1	N: 17 Women: – Age: 60 BMI: 28.3 VAS pain: 76 mm K/L: 3.2	4 weeks of exercise therapy, kinesio tape and LLLT versus 4 weeks of exercise therapy, kinesio tape and sham LLLT	Pain: VAS Disability: – QoL: – Week of assessment: **4**, **8**
Nivbrant 1992[19]	N: 15 Women: 69.2% Age: 69 years BMI: – VAS pain: 67 mm K/L: –	N: 15 Women: 84.6% Age: 66 years BMI: – VAS pain: 58 mm K/L: –	2 weeks of LLLT versus 2 weeks of sham LLLT	Pain: VAS (movement) Disability: Walking disability QoL: – Week of assessment: **2**, 3, **6**

Continued

Table 1 Continued

First author	Intervention group at baseline	Control group at baseline	Intervention versus control programme	Outcome scales, week of reassessment
Rayegani 2012[43]	N: 12 Women: 83.3% Age: 61.7 years BMI: – VAS pain: 63 mm K/L:<4	N: 13 Women: 92.3% Age: 61.2 years BMI: – VAS pain: 52 mm K/L:<4	2 weeks of LLLT versus 2 weeks of sham LLLT	Pain: WOMAC Disability: WOMAC QoL: – Week of assessment: 6, **14**
Tascioglu 2004[40] (3 J)	N: 20 Women: 70% Age: 62.86 years BMI: 27.56 VAS pain: 68 mm K/L: 2	N: 20 Women: 65% Age: 64.27 years BMI: 29.56 VAS pain: 63.88 mm K/L: 2	2 weeks of LLLT versus 2 weeks of sham LLLT	Pain: WOMAC Disability: WOMAC QoL: – Week of assessment: **3**, 26
Tascioglu 2004[40] (1.5 J)	N: 20 Women: 75% Age: 59.92 years BMI: 28.63 VAS pain: 65.72 mm K/L: 2.5	N: 20 Women: 65% Age: 64.27 years BMI: 29.56 VAS pain: 63.88 mm K/L: 2	2 weeks of LLLT versus 2 weeks of sham LLLT	Pain: WOMAC Disability: WOMAC QoL: – Week of assessment: **3**, 26
Youssef 2016[42] (904 nm)	N: 18 Women: 66.7% Age: 67.5 BMI:<40 VAS pain: 51.67 mm K/L: 2	N: 15 Women: 66.7% Age: 66.3 years BMI:<40 VAS pain: 50 mm K/L: 2	8 weeks of exercise therapy and LLLT versus 8 weeks of exercise therapy and sham LLLT	Pain: WOMAC Disability: WOMAC QoL: – Week of assessment: **8**
Youssef 2016[42] (880 nm)	N: 18 Women: 61.1% Age: 67.3 BMI: <40 VAS pain: 52.50 mm K/L: 2	N: 15 Women: 66.7% Age: 66.3 years BMI: <40 VAS pain: 50 mm K/L: 2	8 weeks of exercise therapy and LLLT versus 8 weeks of exercise therapy and sham LLLT	Pain: WOMAC Disability: WOMAC QoL: – Week of assessment: **8**

The values for age and body mass index (BMI) are means and the values for K/L grade are medians. Baseline Visual Analogue Scale (VAS) scores have been extracted or estimated as described in the Method section. Week of assessment in bold denotes time point used for the main meta-analyses.
AQoL-6D, Assessment of Quality of Life 6 Dimensions; DIQ, Disability Index Questionnaire; K/L, Kellgren/Lawrence; LLLT, low-level laser therapy; NRS, Numeric Rating Scale; QoL, quality of life; SKFS, Saudi Knee Function Scale; TENS, Transcutaneous Electrical Nerve Stimulation; VNPS, Visual Numerical Pain Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

weeks with the non-recommended LLLT doses (tables 1 and 2). Non-recommended LLLT doses were applied in nine of the trials. That is, Al Rashoud *et al*,[31] Bülow *et al*,[20] Tascioglu *et al*[40] and Bagheri *et al*[23] applied too few (<4) Joules per treatment spot with 830 nm wavelength, Jensen *et al*,[21] Nivbrant *et al*[19] and Hinman *et al*[41] applied too few (<1) Joules per treatment spot with 904 nm wavelength and Youssef *et al*[42] (one group) and Rayegani *et al*[43] used continuous laser with too long of a wavelength (880 nm; table 2). No adverse event was reported by any of the trial authors. None of the trial authors stated receiving funding from the laser industry (online supplementary material).

Overall, pain was significantly reduced by LLLT compared with the placebo control at the end of therapy (14.23 mm VAS (95% CI 7.31 to 21.14); I^2=93%; n=816; figure 2) and during follow-ups 1–12 weeks later (15.92 mm VAS (95% CI 6.47 to 25.37); I^2=93%; n=581; figure 3). The dose subgroup analyses demonstrated that pain was significantly reduced by the recommended LLLT doses compared with placebo at the end of therapy (18.71 mm (95% CI 9.42 to 27.99); I^2=95%; n=480; figure 2) and during follow-ups 2–12 weeks later (23.23 mm VAS (95% CI 10.60 to 35.86); I^2=95%; n=392; figure 3). The dose subgroup analyses demonstrated that pain was significantly reduced by the non-recommended LLLT doses compared with placebo at the end of therapy (6.34 mm VAS (95% CI 1.26 to 11.41); I^2=44%; n=336; figure 2), but the difference during follow-ups 1–12 weeks later was not significant (6.20 mm VAS (95% CI −0.65 to 13.05); I^2=38%; n=189; figure 3). The between-subgroup differences (recommended versus non-recommended doses) in pain results were significantly in favour of the recommended LLLT doses regarding both time points (p=0.02 and 0.02; figures 2 and 3).

Overall, disability was significantly reduced by LLLT compared with placebo at the end of therapy (SMD=0.59 (95% CI 0.33 to 0.86); I^2=57%; n=617; figure 4) and during follow-ups 1–12 weeks later (SMD=0.66 (95% CI 0.23 to 1.09); I^2=67%; n=289; figure 5). The dose subgroup analyses demonstrated that disability was significantly reduced by the recommended LLLT doses compared with placebo

Table 2 Laser therapy characteristics of the included trials

First author	Treated area	Wavelength (nm)	Joules per treatment spot	Mean output power (mW)	Seconds per treated spot	Number of spots treated	Sessions/sessions per week
Al Rashoud 2014[31]*	Knee joint line (medial and lateral) and acupoints (SP9, SP10, ST36)	830	1.2	30	40	5	9/3
Alfredo 2011, 2018[29 52]	Knee joint line (medial and lateral)	904	3	60	50	9	9/3
Alghadir 2014[32]	Knee condyles, joint line (medial and lateral) and popliteal fossa	850	6	100	60	8	8/2
Bagheri 2011[23]*	Knee joint line	830	3	30	100	10	10/5
Bülow 1994[20]*	Painful spots in 0–10 cm radius of the knee joint line	830	1.5–4.5	25	60–180	5–15	9/3
Delkhosh 2018[39]	Knee joint	830	5	30	167	5	10/5
Fukuda 2011[30]	Front knee capsule	904	3	60	50	9	9/3
Gur 2003[33] (1.5 J)	Anterolateral and anteromedial portal of the knee	904	1.5	10	150	2	10/5
Gur 2003[33] (1 J)	Anterolateral and anteromedial portal of the knee	904	1	11.2	90	2	10/5
Gur and Oktayoglu	Anterolateral and anteromedial portal of the knee	904	1.5	10	150	2	10/5
Gworys 2012[18]	Knee joint line, patellofemoral joint and popliteal fossa	810	8	400	20	12	10/5
Hegedüs 2009[53]	Knee joint line, popliteal fossa and condyles	830	6	50	120	8	8/2
Helianthi 2016[54]	Knee joint line (lateral) and acupoints (ST36, SP9, GB34, EX-LE-4)	785	4	50	80	5	10/2
Hinman 2014[41]*	Acupoints (locations not stated)	904	0.2	10	20	6	8-12/0.67–1
Jensen 1987[21]*	Knee joint line (medial and lateral), apex and basis of patellae	904	0.054	0.3	180	4	5/5
Kheshie 2014[47]†	Front knee	830	–	160	–	–	12/2
Koutenaei 2017[55]	Front knee, popliteal fossa and femur condyles in the popliteal cavity	810	7	100	70	8	10/5
Mohammed 2018[56]	Knee joint line (lateral) and acupoints (ST36, Sp10, GB, ashi)	808	5.4	90	60	7	12/3
Nambi 2016[48]	Knee joint line, condyles and popliteal fossa	904	1.5	25	60	8	12/3
Nivbrant 1992[19]*	Knee joint line (medial and lateral) and acupoints (ST34, SP10, X32)	904	0.72	4	180	7	6/3
Rayegani 2012[43]*	Knee joint line and popliteal fossa	880	6	50	120	8	10/5
Tascioglu 2004[40] (3 J)*	Painful spots on the knee	830	3	50	60	5	10/5
Tascioglu 2004[40] (1.5 J)*	Painful spots on the knee	830	1.5	50	30	5	10/5
Youssef 2016[42] (904 nm)	Knee joint line (medial and lateral)	904	3	60	50	9	16/2
Youssef 2016[42] (880 nm)*	Knee joint line (medial and lateral), epicondyles and popliteal fossa	880	6	50	120	8	16/2

*Non-recommended low-level laser therapy dose.
†1250 Joules per session.

at the end of therapy (SMD=0.75 (95% CI 0.46 to 1.03); I^2=34%; n=339; figure 4) and during follow-ups 2–8 weeks later (SMD=1.31 (95% CI 0.92 to 1.69); I^2=0%; n=129; figure 5). The dose subgroup analyses demonstrated that disability was neither significantly reduced by the non-recommended LLLT doses compared with placebo at the end of therapy (SMD=0.36 (95% CI −0.02 to 0.73); I^2=49%; n=278; figure 4) nor during follow-ups 1–12 weeks later (SMD=0.26 (95% CI −0.06 to 0.58); I^2=0%; n=160; figure 5). The between-subgroup differences in disability results were in favour of the recommended LLLT doses over the non-recommended LLLT doses but only significantly regarding one of two time points (p=0.11 and <0.0001; figures 4–5).

No QoL meta-analysis was performed because this outcome was only assessed in a single trial, that is, by Hinman *et al* who applied a non-recommended LLLT dose and reported insignificant results.[41]

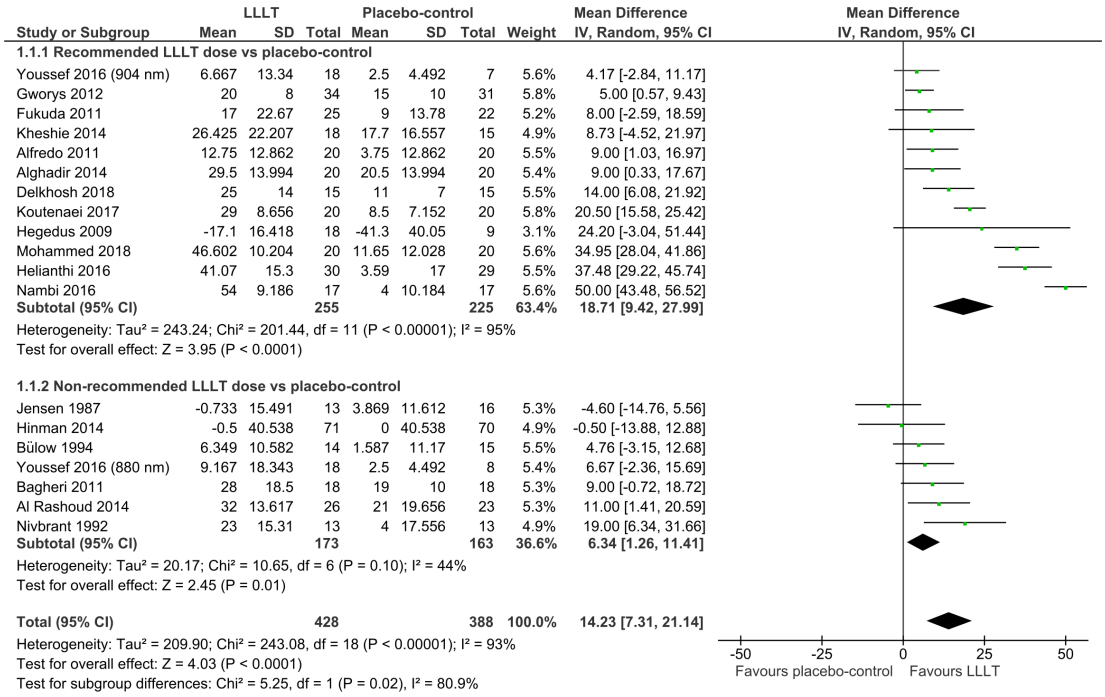

Figure 2 Pain results from immediately after the end of therapy. LLLT, low-level laser therapy.

The funnel plots indicated that there was no publication bias (online supplementary material). We additionally checked for small study bias by reducing the statistical weight of the smallest studies through a change from random to fixed effects models and this led to similar mean effect estimates, indicating that there was no small study bias (online supplementary material).[35]

Methodological quality of the included trials was judged adequate (low risk of bias), unclear (unclear risk of bias) and inadequate (high risk of bias) in 75%, 19% and 6% instances, respectively. Risk of detection bias and reporting bias appeared low in all the trials. There was a lack of information regarding random sequence generation in five trials, allocation concealment in 12 trials, blinding of therapist in four trials and incomplete outcome data in four trials. Therapist blinding was inadequate in seven trials and there was an inadequate handling of data in a single trial (figure 6). However, risk-of-bias subgroup analyses conducted post hoc revealed that there was no statistically significant interaction between the effect estimates and risk of bias, and the analyses did not display a drop in statistical heterogeneity (online supplementary material). Support for our risk of bias judgments is available (online supplementary material).

Neither did the levels of statistical heterogeneity change when we switched from the MD to the SMD method post hoc (online supplementary material).

Post hoc analyses demonstrated that LLLT was significantly superior to placebo both with exercise therapy (p=0.0009 for pain and p<0.0001 for disability) and without exercise therapy (p=0.01 for pain and p=0.008

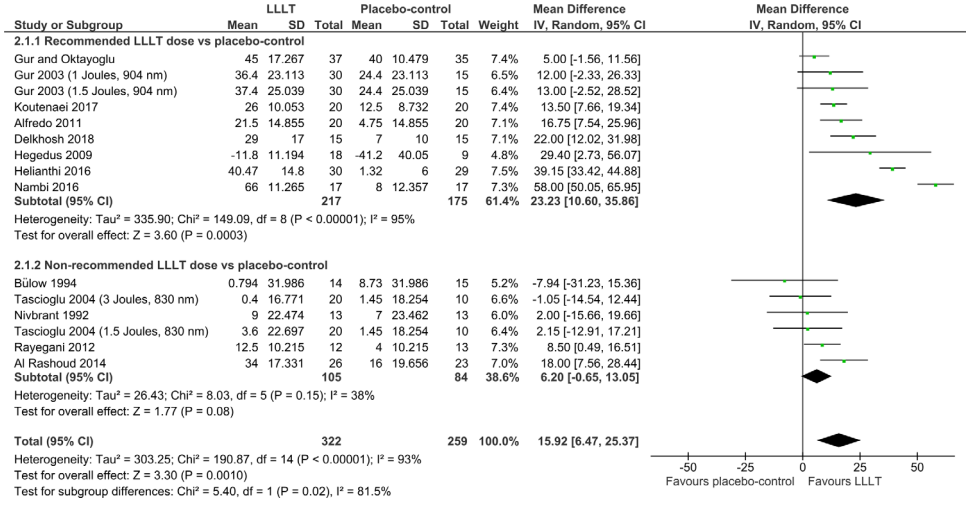

Figure 3 Pain results from follow-ups 1–12 weeks after the end of therapy. LLLT, low-level laser therapy.

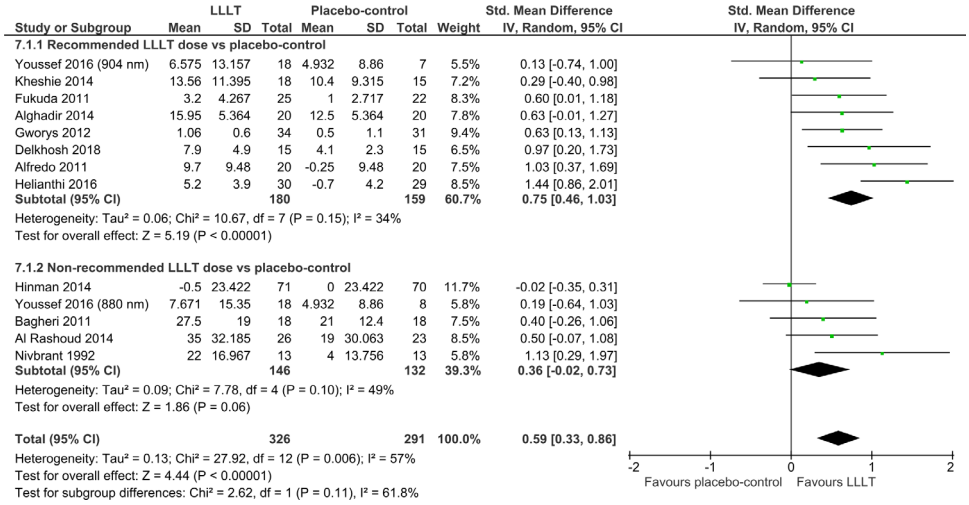

Figure 4 Disability results from immediately after the end of therapy. LLLT, low-level laser therapy.

for disability) as cointervention (online supplementary material).

Post hoc analyses were performed to more precisely estimate the pain time-effect profile for the recommended LLLT doses by imputing the results of the trials with these doses in subgroups with narrower time intervals. Pain was significantly reduced by the recommended LLLT doses compared with placebo immediately after therapy weeks 2–3 and 4–8 and at follow-ups 2–4, 6–8 and 12 weeks later; the peak point was 2–4 weeks after the end of therapy (31.87 mm VAS beyond placebo (95% CI 18.18 to 45.56); I^2=93%; n=322). The 21-week and 34-week follow-up pain results were not statistically significant (figure 7 and online supplementary material). The statistical heterogeneity in the main pain analyses of the recommended LLLT doses was high (I^2=95%; figures 2–3) but the mean statistical heterogeneity of the five subgroups covering the same time period was only moderate (I^2=58%; figure 7 and online supplementary material).

DISCUSSION

Our meta-analyses showed that pain and disability were significantly reduced by LLLT compared with placebo. We subgrouped the included trials according to the WALT recommendations (2010) for laser dose per treatment spot, and this revealed a significant dose–response relationship. Our principal finding is that the recommended LLLT doses offer clinically relevant pain relief in KOA. The non-recommended LLLT doses provided no or little positive effect.

The absolute minimally clinically important improvement (MCII) of pain in KOA has been estimated to be 19.9, 17 and 9 units on a 0–100 scale in 2005, 2012 and 2015, respectively.[44–46] It is important to note that the MCII of pain is a within-subject improvement and depends on baseline pain intensity.[44–46] The pain reduction from the recommended LLLT doses was significantly superior to placebo even at follow-ups 12 weeks after the end of therapy, and the difference was greater than 20 mm VAS from the final 4–8 weeks of therapy through follow-ups 6–8 weeks after the end of therapy. Interestingly, the pain reduction from the recommended LLLT doses peaked at follow-ups 2–4 weeks after the end of therapy (31.87 mm VAS highly significantly beyond placebo).

Disability was also significantly reduced by the recommended LLLT doses compared with placebo, that is, to

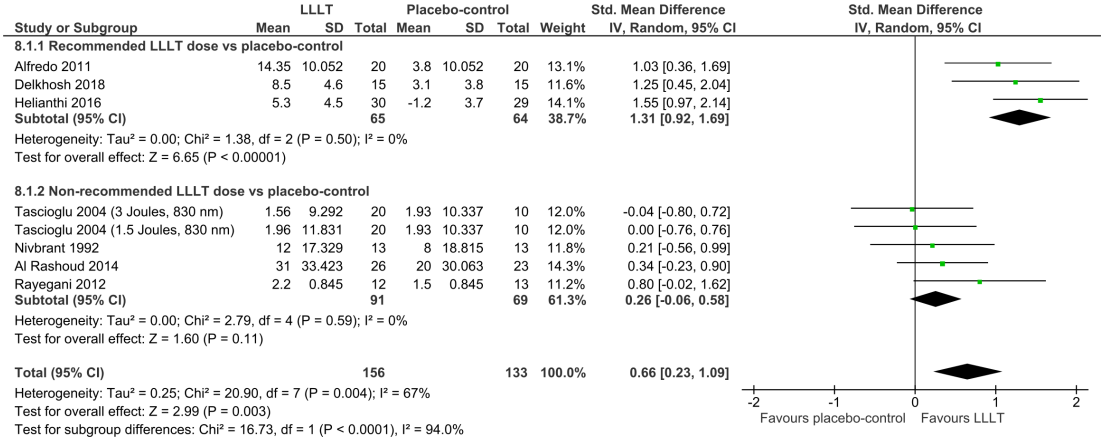

Figure 5 Disability results from follow-ups 1–12 weeks after the end of therapy. LLLT, low-level laser therapy.

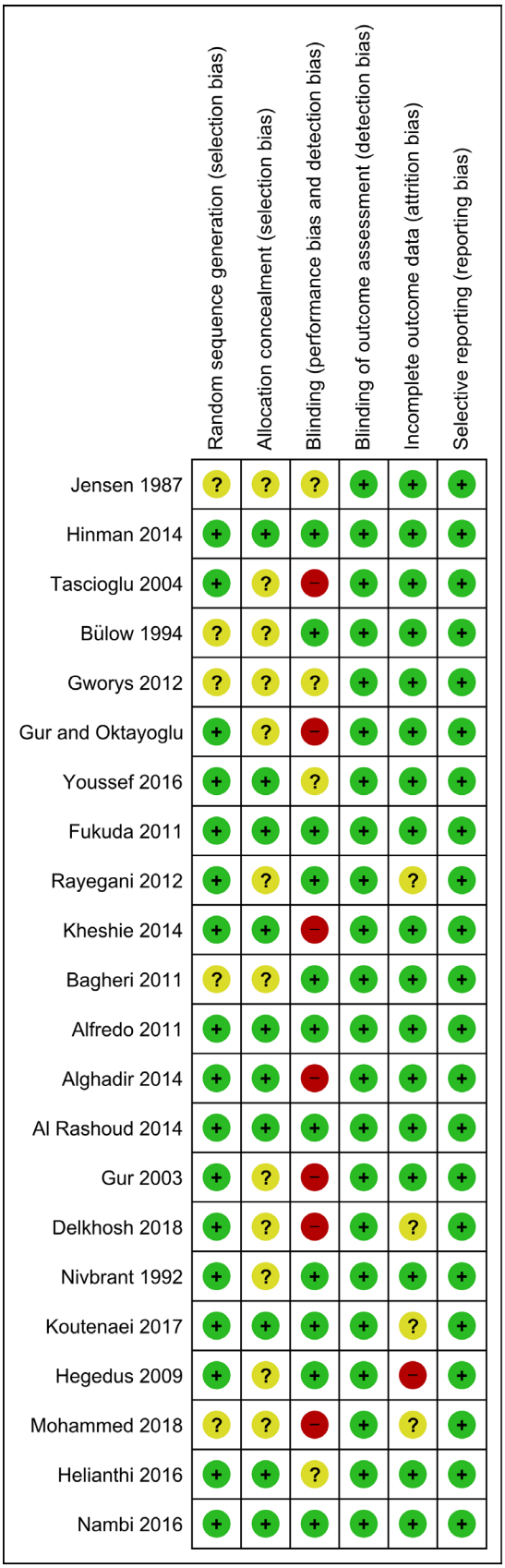

Figure 6 Risk-of-bias plot of the included trials. The trials are ranked by mean pain effect estimates, that is, more laser positive results in the bottom of the figure; the plot is based on the results from the main pain analyses (immediately after the end of therapy, primarily).

a moderate extent at the end of therapy (SMD=0.75) and to a large extent during follow-ups 2–8 weeks later (SMD=1.31). More trials with disability assessments are needed to precisely estimate the effect of LLLT on this outcome during follow-up.

Furthermore, our analyses demonstrated that LLLT is effective in KOA both with and without exercise therapy as cointervention. Strength training was seemingly only used as an adjunct to LLLT in two of the included trials,[47 48] and thus more trials with this combination of treatments are needed.

Risk of bias of the included trials appeared insignificant and could not explain the statistical heterogeneity (online supplementary material). We find it plausible that some of the statistical heterogeneity of the overall analyses is associated with the dose subgroup criteria (wavelength-specific laser doses per treatment spot) since the mean levels of statistical heterogeneity of the subgroup analyses were consistently lower than the overall levels. It is unknown to us whether other differences in the LLLT protocols impacted the results.

The statistical heterogeneity in the main pain analyses of the recommended LLLT doses was high, and some of it can be explained by the pooling of results from various time points of assessment given the pain reduction increased and subsequent decreased with time; the pain reduction time profile showed a drop in statistical heterogeneity to a moderate level.

According to WALT, the osteoarthritic knee should be laser irradiated to reduce inflammation and promote tissue repair.[24 25 49] One of the discrepancies from our review and previously published reviews of the same topic is that we omitted the RCT by Yurtkuran *et al*,[8 17 28 50] as they solely applied laser to an acupoint located distally from the knee joint (spleen 9).

In line with our findings and the WALT dose recommendations, Joensen *et al*[26] observed that the percentage of laser penetrating rat skin at 810 and 904 nm wavelength was 20% and 38%–58%, respectively. That is, to deliver the same dose beneath the skin, 2.4 times the energy on the skin surface is required with an 810 nm laser compared with a 904 nm laser device. This may be due to the different wavelengths and/or because 904 nm laser is superpulsed (pulse peak power ≥10 000 mW typically), whereas shorter wavelength laser is delivered continuously or with less intense pulsation.[26] The estimated median dose applied with the recommended LLLT was 6 and 3 J per treatment spot with 785–860 and 904 nm wavelength laser, respectively. Most of the trial authors reported LLLT parameters in detail but did not state whether the laser devices were calibrated. Therefore, in the LLLT trials with non-significant effect estimates, equipment failure cannot be ruled out.

It is important to note that no adverse events were reported by any of the trial authors and the dropout rate was minor, indicating that LLLT is harmless.

Our clinical findings that the effect of LLLT progresses over time is in line with in vivo results of Wang *et al*.[12] The

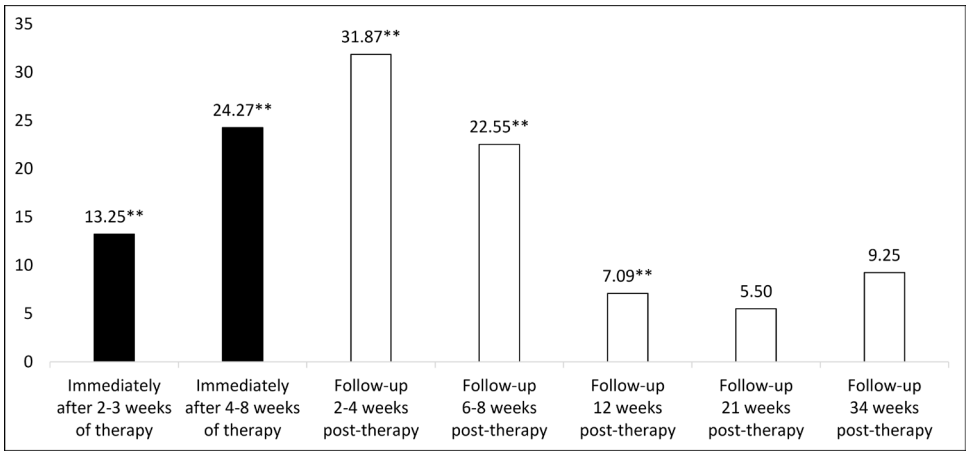

Figure 7 Pain time-effect profile (recommended low-level laser therapy (LLLT) doses versus placebo-control). Values on the y-axis are mm Visual Analogue Scale (VAS) pain results. Positive VAS score indicates that the recommended LLLT doses are superior to placebo. The related forest plot is available (online supplementary material). **The recommended LLLT doses are highly statistically significantly superior to placebo (p≤0.01).

positive effect from LLLT seems to last longer than those of widely recommended painkiller drugs.[51] The effect of using the NSAID tiaprofenic acid, for example, is probably gone within a week, unless the treatment is continued.[51] Future trials should investigate whether booster sessions of LLLT can prolong the positive effect. Comparative cost-effectiveness analyses of LLLT and NSAIDs would also be of great interest.

Strengths and limitations of this study

In contrast to previous reviews on the current topic, our review was conducted in conformance with an a priori published protocol,[8 17 28] which included a detailed plan for statistical analysis (eg, laser dose subgroup criteria). Furthermore, this is the first review on this topic without language restrictions,[8 17 28] and this expansion proved important since four (18%) of the included trials were reported in non-English language.[19 21 23 39]

We conducted a series of meta-analyses illustrating the effect of LLLT on pain over time. To ensure high reproducibility of the meta-analyses, three persons each independently extracted the outcome data from the included trial articles.

This review is not without limitations. It lacks QoL analyses, a detailed disability time-effect analysis and direct comparisons between LLLT and other interventions.

CONCLUSIONS

LLLT reduces pain and disability in KOA at 4–8 J with 785–860 nm wavelength and at 1–3 J with 904 nm wavelength per treatment spot.

Contributors MBS, JMB and HL wrote the PROSPERO protocol. MBS and JMB selected the trials, with the involvement of IFN when necessary. MBS and JJ judged the risk of bias, with the involvement of IFN when necessary. MBS and IFN did the translations. MBS, JMB and KVF extracted the data. MBS performed the analyses, under supervision of JMB. All the authors participated in interpreting of the results. MBS drafted the first version of the manuscript, and subsequently revised it, based on comments by RÁBL-M, HS and all the other authors. All the authors read and accepted the final version of the manuscript.

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Competing interests JMB and RÁBL-M are post-presidents and former board members of World Association for Laser Therapy, a non-for-profit research organization from which they have never received funding, grants or fees. The other authors declared that they had no conflict of interests related to this work.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The dataset for meta-analysis is available from the corresponding author upon reasonable request. The corresponding author affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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