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**Effects of low-level laser therapy on pain in patients with musculoskeletal disorders – a systematic review and meta-analysis.**

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**Abstract**

INTRODUCTION: This meta-analysis investigated the effectiveness of low-level laser therapy (LLLT) on pain in adult patients with musculoskeletal disorders.

EVIDENCE ACQUISITION: A systematic literature search was conducted in the Medline and PEDro databases. Two researchers independently screened titles and abstracts of the retrieved studies for eligibility. Quality assessment of the eligible studies was conducted using the PEDro rating scale. Studies that scored ≥ 4 were included. A random-effects model was used for this meta-analysis. Subgroup meta-analyses were conducted to evaluate the influence of the adherence of the applied LLLT to the World Association of Laser Therapy (WALT) guidelines, the anatomical site under investigation and the study design on the overall weighted mean effect size. Meta regression was used to assess the possible influence of the study quality on the individual study effect sizes.

EVIDENCE SYNTHESIS: Eighteen studies allowing for 21 head-to-head comparisons (totaling n=1462 participants) were included. The pooled raw mean difference ($D$) in pain between LLLT and the control groups was -0.85 [95%CI: -1.22 to -0.48]. There was high ($I^2$ = 85.6%) and significant between study heterogeneity (Cochran's $Q$ = 139.2; df = 20; $p <$ 0.001). The subgroup meta-analysis of the comparisons not following the WALT guidelines revealed a $D$ = -0.68 [95%CI: -1.09 to -0.27]. In this group, heterogeneity decreased to $I^2$ = 72.6% (Q = 51.2; df = 14; $p < 0.001$). In the WALT subgroup $D$ equaled -1.52 [95%CI: -2.34 to -0.70]. This between groups difference was clinically relevant although statistically not significant (Q = 3.24; df = 1; $p = 0.072$).

CONCLUSION: This meta-analysis presents evidence that LLLT is an effective treatment modality to reduce pain in adult patients with musculoskeletal disorders. Adherence to WALT dosage recommendations seems to enhance treatment effectiveness.

**Key words:** Low-level light therapy - Meta-analysis - Musculoskeletal diseases - Systematic review

## Introduction

In musculoskeletal rehabilitation, low-level laser therapy (LLLT) is frequently used as an adjunct in the management of pain in patients with musculoskeletal disorders.[1,2]

LLLT refers to a non-invasive, phototherapy or photobiomodulation that uses photons at a non-thermal irradiance to stimulate biological activity and has been classified as a safe, non-invasive treatment modality.[3]

Indeed, several possible mechanisms have been attributed to LLLT such as: increased endogenous opioid neurotransmitter production[4], raised threshold to thermal pain and enhanced local blood circulation[5,6], increased oxygen consumption by accelerating the redox reaction rate of the electron respiratory chain of mitochondria[7], increased adenosine triphosphate (ATP) production at the cellular level[8-10], increased production of anti-inflammatory cytokines. [11-13]

Although LLLT is used in a variety of clinical settings, controversial results on its effectiveness in the treatment of pain in patients with musculoskeletal disorders have been reported.[14-17]

These conflicting results can be explained by the following facts: (1.) the underlying cellular photobiostimulating mechanisms of LLLT are not well understood with as a consequence a largely empirical use and (2.) the complexity of the appropriated parameter selection before each treatment session.[3,18] Therefore, an essential factor for the effective administration of LLLT is the certainty of optimal dosing to reach a sufficient volume of pathological target tissue.[19] Although the World Association of Laser Therapy (WALT) introduced evidence based dosage recommendations for optimal administration of LLLT in the treatment of musculoskeletal pain[19], there are still RCT studies published without applying the WALT recommendations in their treatment protocol.[14-17,20-27] This can lead to low treatment efficacy (Fig.1). [17,24]

[Insert figure 1. (Forest-plot) somewhere here please]

Figure 1. Forest plot of the 18 trials (21 head-to-head comparisons) evaluating the effects of LLLT on pain versus control in patients with musculoskeletal disorders and subgroup analysis of adherence to WALT guidelines.

## Evidence acquisition

This study was performed following the guidelines on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Inclusion and exclusion criteria were set a priori. Eligible for inclusion were clinical trials, RCTs, reviews, meta-analyses, practice guidelines, studies on adult humans, published during the past five years in the English or German language. Only studies comparing LLLT versus a sham/placebo LLLT or studies comparing usual therapy + LLLT versus usual therapy were selected. Studies on the use of LLLT in the context of mandibular joint disorders were excluded. VAS was used to quantify pain in all studies.[28,29]

### *Outcomes*

Within the context of evidence based practice this systematic review and meta-analysis aimed to answer the following questions:

1. Is LLLT effective in treatment of pain in patients with musculoskeletal disorders?
2. What is the effect of implementing the WALT dosage recommendations on the overall effect size?
3. Is the pain relieving effect of LLLT affected by the anatomical site of the lesion?
4. Does the study design or methodological study quality influence the individual effect size?

*Data sources and search strategies*

An electronic search was conducted in the MEDLINE (PubMed) and PEDro (Physiotherapy Evidence Database) databases with a latest update on 11.11.2015. Based on the PICO acronym, the following search algorithm was developed to evaluate the effects of LLLT in patients with musculoskeletal problems:

((((("musculoskeletal diseases"[MeSH Terms] AND "low-level light therapy"[MeSH Terms] OR ("low-level light therapy"[MeSH Terms] OR ("low-level"[All Fields] AND "light"[All Fields] AND "therapy"[All Fields]) OR "low-level light therapy"[All Fields] OR "lllt"[All Fields])) OR (Low-power[All Fields] AND ("lasers"[MeSH Terms] OR "lasers"[All Fields] OR "laser"[All Fields]))) OR (Low-intensity[All Fields] AND ("lasers"[MeSH Terms] OR "lasers"[All Fields] OR "laser"[All Fields]))) OR (low-laser[All Fields] AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]))) AND ("placebos"[MeSH Terms] OR "placebos"[All Fields] OR "placebo"[All Fields])) NOT ("temporomandibular joint"[MeSH Terms] OR ("temporomandibular"[All Fields] AND "joint"[All Fields]) OR "temporomandibular joint"[All Fields] OR "tmj"[All Fields]) AND (Clinical Trial[ptyp] AND hasabstract[text] AND "2011/07/01"[PDat] : "2016/06/28" [PDat] AND "humans"[MeSH Terms]).

Manual searching and searching conference books of abstracts was not conducted. Pain was the outcome of interest in this study. In case of incomplete data reporting, the corresponding author of a study was contacted to obtain the missing data. A trial would be excluded from the meta-analysis if authors did not react to the request.

*Study selection*

Two researchers (AB and RC) independently screened titles and abstracts of the retrieved studies for their eligibility. Agreement was achieved by consensus. The reference lists of interpretation of the results.

The 95% confidence intervals [95%CI] for the individual study effect sizes as well as the overall weighted mean were calculated.

Mixed effects subgroup analyses were conducted to evaluate the influence of co-variates, such as the adherence of the applied LLLT to the WALT dosage guidelines, anatomical site under investigation and the study design. Meta regression was used to assess the possible influence of the study quality on the individual study effect sizes.

The Cochran's $Q$ statistic and its corresponding $p$-value were calculated to test the hypothesis that there was no heterogeneity across the individual effect sizes. $I^2$ was calculated to assess the degree of heterogeneity across studies. Higgins' suggested bench marking values were applied for the interpretation of the observed heterogeneity. Publication bias was assessed using visual analysis of the funnel plot and by formal testing for funnel plot asymmetry using the 'trim and fill' and the 'fail 'n safe' algorithms. For all analyses, $p$-values less than 0.05 were considered significant. All calculations and plots were conducted using the CMA-2 software (Comprehensive Meta-Analysis 2nd version, Biostat, Englewood, NJ, USA).

**Evidence synthesis**

*Study characteristics*

Our search resulted in the identification of 124 potentially relevant studies. Three studies were suggested by experts and added in the further processing. After removing duplicates, the initial search yielded 94 articles which were screened on title, abstract and full-text. A total of 19 studies fulfilled the a priori set inclusion criteria (Fig.2). From the total of n=1462 participants, n=768 were in the LLLT group and n=694 in the control group. Gender distribution was reported in 19 comparisons (overall females: n=848; males: n= 528) while this information could not be revealed from one study. [14]

In five of the 19 studies, the reviewers independently agreed on all the items of the inclusion and exclusion criteria. One study[30] showed important methodological limitations (PEDro score = 2) and, therefore, was excluded from the further analysis.

[Insert figure 2. somewhere here please]

Figure 1. Flow chart of the study selection process.

Thus, 18 studies with a PEDro score ranging from 5 to 10 remained for the quantitative analysis. Three studies showed to be more-armed studies.[14,17,26] The arms were included as separate head-to-head comparisons, totaling the number of comparisons in the meta-analysis to 21 (table 1.).

[Insert table 1. somewhere here please]

Legend Table 1. NSAID = nonsteroidal anti-inflammatory drugs, LLLT = low-level laser therapy, VAS = visual analog scale.

*Comparison 1: What is the effect of low-level laser therapy on pain compared to control in patients with musculoskeletal disorders?*

All 21 comparisons analyzed the effect of LLLT on pain in patients with musculoskeletal disorders (Table 1). The results were extracted from the studies and were analyzed using the random-effects model because of the expected high heterogeneity between studies. The overall weighted raw mean difference ($D$) in pain between LLLT and the control groups was 0.85 [95%CI: -1.22 to -0.48] ($p < 0.001$). Heterogeneity analysis showed high ($I^2 = 85.6\%$) and significant between study heterogeneity (Cochran's $Q = 139.2$; df = 20; $p < 0.001$).

Despite the observed inconsistency in the effect size of LLLT on pain, the present meta-analysis presents good evidence for the use of LLLT in the treatment of pain in adult patients with musculoskeletal disorders. From the 21 head-to-head comparisons, 17 favored LLLT while four comparisons (extracted from three studies) reported no beneficial effects of LLLT on pain (Fig. 1).

Figure 3 depicts the funnel plot of standard error by *D*. The classic 'fail-safe N' algorithm showed that 1179 non-significant studies would be needed to increase the *p*-value above the set alpha level of 0.05, indicating that there was but very low risk for publication bias.

[Insert figure 3 (funnel plot) somewhere here please]

Figure 3. Funnel plot of the included studies.

*Comparison 2: Does implementing the WALT dosage recommendations affects the overall effect size?*

Six of the analyzed studies followed the 2005 published WALT guidelines for the LLLT intervention.[19] To test if adherence to WALT guidelines had an effect on the overall weighted raw mean difference a subgroup meta-analysis was conducted. Subgroup meta-analysis showed no significant relationship between the positive pain relieving effects and the use of WALT treatment dosage recommendations. Interestingly, only six studies (table 1.) implemented the WALT dosage recommendations whilst a large variety in reported dose and beam parameter was used. The subgroup meta-analysis of the 15 head-to-head comparisons described in the studies which did not follow the WALT guidelines revealed a mean change in VAS of $D$ = -0.68 [95%CI: -1.09 to -0.27]. In this group, heterogeneity decreased to $I^2$ = 72.6% (Q = 51.2; df = 14; $p < 0.001$). In the WALT subgroup, the mean change in VAS equaled $D$ = -1.52 [95%CI: -2.34 to -0.70]. Under random-effects conditions, the between groups difference was statistically not significant at the 5% level (Q = 3.24; df = 1; $p$ = 0.072).

*Comparison 3: Is the pain relieving effect of LLLT affected by the anatomical site of the lesion?*

In the 21 head-to-head comparisons included in the 18 studies, the effect of LLLT on pain in patients with musculoskeletal disorders was investigated at nine different anatomical sites:

back (k = 4), elbow (k = 1), foot (k = 1), hand (k = 1), knee (k = 4), neck (k = 1), perineal (k = 1), shoulder (k = 3), wrist (k = 5). To test if LLLT had different effects on pain at the different anatomical sites another subgroup meta-analysis was conducted. For the subgroups including more than one study per anatomical site, LLLT had the strongest effect on pain in patients with knee disorders with $D$ = -1.34 [95%CI: -2.88 to 0.20], followed by wrist disorders with $D$ = -1.22 [95%CI: -2.05 to -0.39], shoulder disorders with $D$ = -0.76 [95%CI: -1.19 to -0.33] and back disorders with $D$ = -0.63 [95%CI: -1.48 to 0.23]. Under random-effects conditions, the between groups difference was statistically not significant at the 5% level (Q = 13.51; df = 8; $p$ = 0.096).

*Comparison 4: Does the methodological study quality influence the individual effect size?*

A subgroup meta-analysis comparing RCT versus CT studies was conducted. The RCT studies yielded an overall weighted raw mean difference of $D$ = -0.82 [95%CI: -1.23 to -0.40] while the overall weighted effect size in the CT subgroup was $D$ = -1.45 [95%CI: -2.40 to -0.51]. Again, the between groups difference was statistically not significant at the 5% level (Q = 1.45; df = 1; $p$ = 0.228).

To test for an eventual effect of the study quality on the effect size, individual studies effect-sizes were meta-regressed over their Pedro-score which yielded a slope estimate of -0.086 [95%CI: -0.16 to -0.01].

**Discussion**

This systematic review and meta-analysis of 21 head-to-head comparisons extracted from 18 studies (totaling n=1462 participants) was conducted to assess the available clinical evidence for the use of LLLT in the treatment of pain in adult patients with musculoskeletal disorders. The secondary objectives were to determine if the study outcome was affected by the adherence to the WALT dosage recommendations, if the pain relieving effect of LLLT was related to the anatomical site of the affected structure, and finally if the observed effect size was influenced by study design or study quality.

In the included studies a large variety in reported dose and beam parameter was used, this observed heterogeneity is in line with the findings of Jenkins et al. (2011) who stated that LLLT effectiveness studies frequently lack in accurate and complete reporting of technical and treatment parameters and that there is a need for more standardized reporting of these parameters.[31] Standardized reporting of beam and treatment parameters and the adherence to the evidence based WALT guidelines will significantly enhance the reproducibility and the body of knowledge on clinical application of LLLT.

Although the between group difference of the effects of adherence to the WALT guidelines did not reach statistical significance, this difference seems to be of important clinical relevance. Several authors have investigated the clinical effectiveness of VAS score reduction by defining the minimum clinically important difference (MCID) on the VAS pain score for a treatment intervention. Todd et al. (1996) stated that a VAS reduction of 13 mm was perceived as clinically relevant in patients with acute trauma pain, while Gallagher et al. (2002) concluded an MCID of 16 mm to be of clinical relevance in patients with acute abdominal pain.[32,33] In the present meta-analysis, a clinical relevant difference of 15.2 mm was found in the LLLT interventions following WALT guidelines. The absence of between groups significance could be the result of the low number of included studies and study subjects.

The studies investigating the effect of LLLT treatment on pain in adult patients with musculoskeletal disorders showed a high variety of anatomical treatment sites. The present meta-analysis suggests that the beneficial effects of LLLT on pain seem to be independent from the anatomical lesion site as the analysis of the between group difference reached no statistical significance.

To see if the overall weighted mean effect was affected by the study type, a subgroup meta-analysis comparing RCT versus CT studies was conducted, yielding no significant difference between the two study types. Despite the methodological flaws in reporting of technical and treatment parameters, the methodological quality spectrum of the included studies ranged from Pedro score 5 to 10 which can be interpreted as moderate to good methodological quality. The regression of the Pedro score on the study effect size reached no significance indicating that the conflicting evidence regarding the effectiveness of LLLT in the treatment of pain in patients with musculoskeletal disorders can only be partially explained by the methodological quality of the studies.

This meta-analysis suggests that remaining strictly to WALT guidelines during treatment may affect the clinical pain relieving outcome. Hence, therapists applying LLLT for the pain relief treatment of patients with musculoskeletal disorders, should prefer the use of evidence based treatment strategies and WALT dosage recommendations to optimize treatment effect. Future studies evaluating the effect of LLLT in the treatment of patients with musculoskeletal disorders should be conducted using standardized beam and treatment parameters to enhance reproducibility and the body of knowledge on the clinical application of LLLT.

A strength of the present study is the systematic review of the literature yielding an important number of clinical trials and randomized clinical trials of moderate to high methodological quality, all assessing pain on the same scale. This allowed for a quantitative analysis by pooling the individual study effect sizes expressed in their original units (i.e. mm on VAS) facilitating the interpretation of the results for the clinician. Furthermore, an analysis of the influence of co-variates such as adherence to the WALT dosage recommendations and anatomical sites on the overall weighted effect size was conducted, providing information with important clinical relevance.

Limitations that may hamper the outcome of this study should be mentioned also. In the fast technical developing field of LLLT, the authors choose to provide an actual status of the evidences for LLLT including only studies of the last five years. We acknowledge that this is another limitation of this study. Beside Medline only one specific physiotherapy database (PEDro) was searched while a grey literature search was omitted. Despite this limitation, the meta-analysis showed but very low risk for publication bias.

**Conclusion**

Based on the results of this study, LLLT appears to be an effective treatment modality to achieve pain relief in adult patients with musculoskeletal disorders. Therapists applying LLLT should follow the WALT dosage recommendations to yield clinically significant better pain relieving effects when treating patients with musculoskeletal disorders. Although the included studies showed a high heterogeneity in anatomical treatments sites, the beneficial effect of LLLT on pain seem to be unaffected by the anatomical site of the lesion.

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Table 1. Characteristics of the included studies

| ***Author / year*** | ***Diagnosis*** | ***n*** | ***Gender distribution*** | ***exp./ contr.*** | ***intervention*** | ***Outcome parameter*** | ***Pedro score*** | ***WALT Dosage Recommendations*** |
|---|---|---|---|---|---|---|---|---|
| Abrisham et al. (2011)[16] | subacromial syndrome | 80 | 30 males / 50 females | 40 / 40 | LLLT & exercise vs. placebo LLLT & exercise | VAS for pain, ROM | 9/10 | No |
| Al Rashoud et al. (2013)[17] | osteoarthritis knee | 49 | 31 males / 18 females | 26 / 23 | LLLT & exercise vs. placebo LLLT & exercise | VAS for pain, ROM | 6/10 | No |
| Alfredo et al. (2011)[18] | osteoarthritis knee | 40 | 9 males / 31 females | 20 / 20 | LLLT & exercise vs. placebo LLLT & exercise | VAS for pain, ROM, muscle strength, Lequesne for functionality, WOMAC questionnaire for Activity | 8/10 | No |
| Ay et al. (2010)[11] (acute) | acute low back pain | 40 | 14 males / 26 females | 20 / 20 | LLLT & hot-pack vs. placebo LLLT & hot-pack | VAS and Likert scale for pain, ROM, Roland Disability Questionnaire & Modified Oswestry Disability Questionnaire for function | 8/10 | No |
| Ay et al. (2010)[11] (chronic) | chronic low back pain | 40 | 20 males / 20 females | 20 / 20 | LLLT & hot-pack vs. placebo LLLT & hot-pack | VAS and Likert scale for pain, ROM Roland Disability Questionnaire & Modified Oswestry Disability Questionnaire for function | 7/10 | No |
| Dogan et al. (2010)[10] | subacromial impingement | 52 | 19 males / 33 females | 30 / 22 | LLLT & cold-pack & exercise vs. placebo LLLT & cold-pack & exercise | VAS for pain, ROM, Shoulder Pain and Disability Index for functional status | 9/10 | No |
| Emanet et al. (2010)[19] | lateral epicondylitis | 46 | 13 males / 33 females | 23 /23 | LLLT & exercise vs. placebo LLLT & exercise | VAS for pain, tenderness (pressure algometry), Painless grip strength (dynamometry) | 6/10 | Yes |
| Fusakul et al. (2014)[20] | carpal tunnel syndrome | 112 | 58 males / 54 females | 56 / 56 | LLLT & neutral wrist splint vs. placebo LLLT & neutral wrist splints | VAS for pain, SSS symptom severity scale, FSS functional status scale, pinch strength, grip strength | 8/10 | Yes |
| Jiang et al. (2011)[8] (mild CTS) | carpal tunnel syndrome | 54 | NM | 27 / 27 | LLLT vs. placebo LLLT | VAS for pain, Boston Questionnaire scale for discomfort symptoms of CTS, Phalen's maneuver & Tinel's sign test for neurological signs of CTS, NCS nerve conduction study | 7/10 | No |

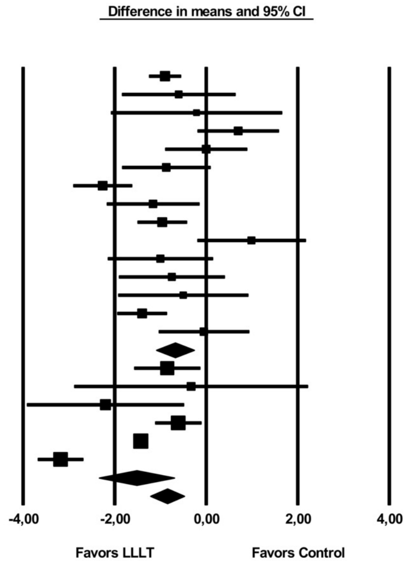
Table 1. Characteristics of the included studies (Continues)

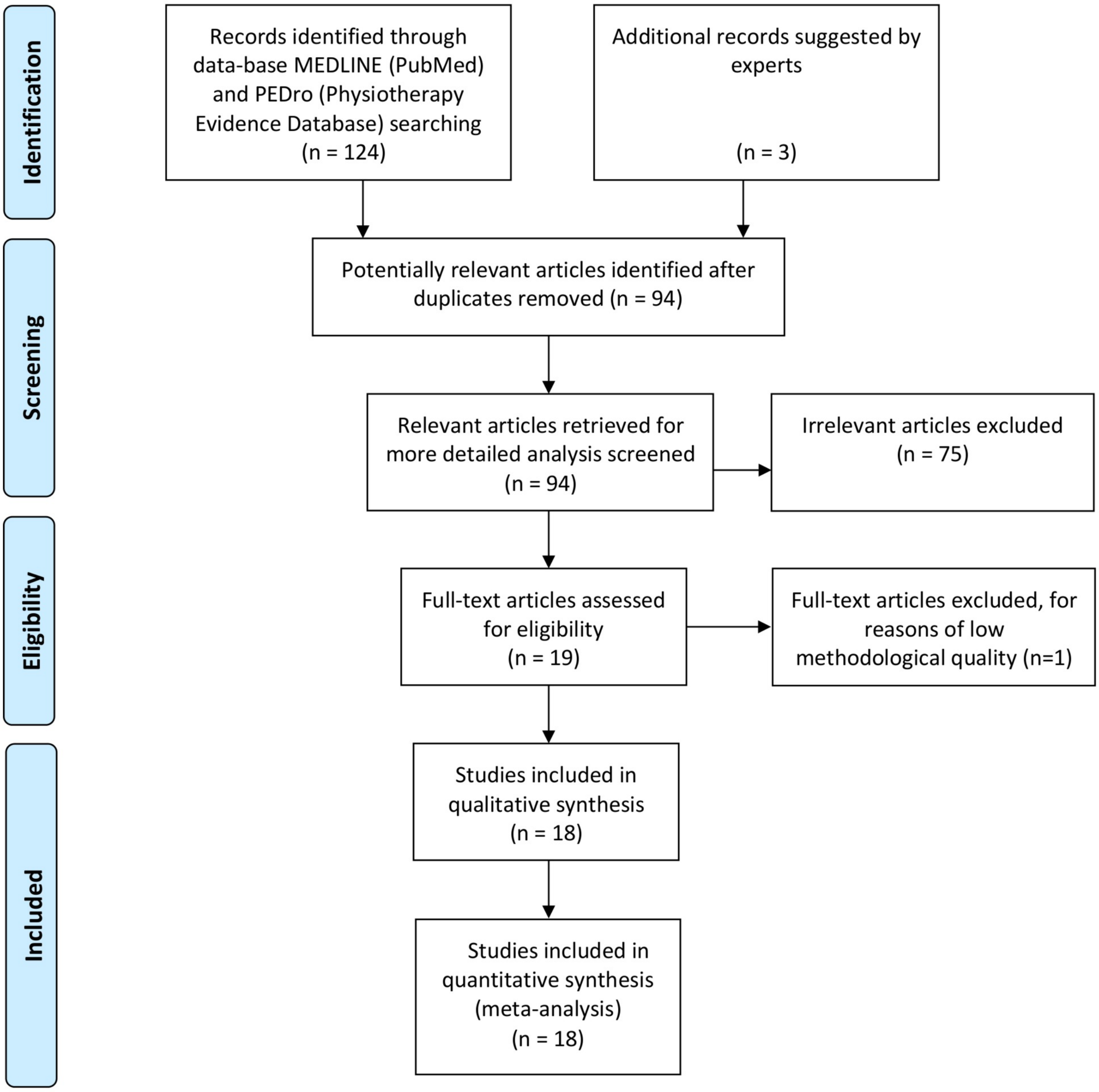
| *Author / year* | *Diagnosis* | *n* | *Gender distribution* | *exp./ contr.* | *intervention* | *Outcome parameter* | *Pedro score* | *WALT Dosage Recommendations* |
|---|---|---|---|---|---|---|---|---|
| Jiang et al. (2011)[8] (moderate CTS) | carpal tunnel syndrome | 33 | NM | 18 / 15 | LLLT vs. placebo LLLT | VAS for pain, Boston Questionnaire scale for discomfort symptoms of CTS, Phalen's maneuver & Tinel's sign test for neurological signs of CTS, NCS nerve conduction study | 7/10 | No |
| Kheshie et al. (2014)[21] | osteoarthritis knee | 53 | 53 males / 0 females | 38 /15 | High-intensity laser therapy & exercise vs. LLLT & exercise vs. placebo LLLT & exercise | VAS for pain, WOMAC scale for knee joint function | 7/10 | No |
| Kiritsi et al. (2010)[22] | plantar fasciitis | 25 | 10 males / 15 females | 15 / 10 | LLLT vs. placebo LLLT | VAS for pain, Ultrasonography for plantar fascia thickness | 7/10 | Yes |
| Konstantinovic et al. (2010a)[23] | acute neck pain | 60 | 25 males / 35 females | 30 / 30 | LLLT vs. placebo LLLT | VAS for pain, neck disability index for neck mobility, SF-12 questionnaire health survey | 10/10 | Yes |
| Konstantinovic et al. (2010b)[24] | low back pain with radiculopathy | 546 | 231 males / 315 females | 182 / 182 | LLLT & NSAID vs. NSAID vs. placebo LLLT & NSAID | VAS for pain, modified Schober test for lumbar mobility, Oswestry disability scale for daily activities, SF-12 questionnaire health survey | 10/10 | Yes |
| Malliaropoulos et al. (2013)[25] | meniscal pathology | 64 | 20 males / 44 females | 32 / 32 | LLLT vs. placebo LLLT | VAS for pain, Lysholm Knee Scoring System for knee function, pain and swelling | 9/10 | Yes |
| Meireles et al. (2010)[26] | rheumatoid arthritis | 78 | 2 males / 76 females | 41 / 37 | LLLT & NSAID vs. placebo LLLT & NSAID | VAS for pain, HAQ (Health Assessment Questionnaire) and DASH questionnaire (Disabilities of the arm shoulder and hand) | 10/10 | No |
| Santos et al. (2012)[27] | episiotomy | 52 | 0 males / 52 females | 26 / 26 | LLLT vs. placebo LLLT | VAS for pain, REEDA scale for healing process | 8/10 | No |

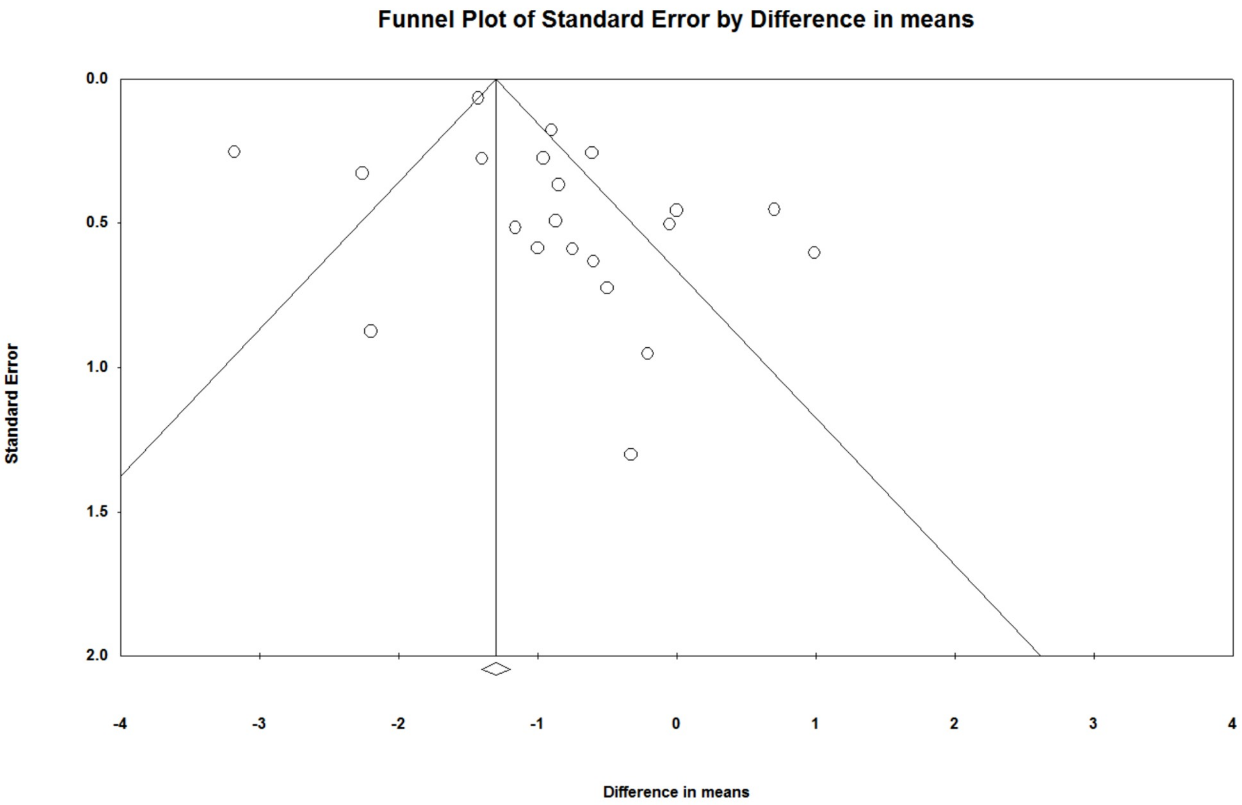
Table 1. Characteristics of the included studies (Continues)

| ***Author / year*** | ***Diagnosis*** | ***n*** | ***Gender distribution*** | ***exp./ contr.*** | ***intervention*** | ***Outcome parameter*** | ***Pedro score*** | ***WALT Dosage Recommendations*** |
|---|---|---|---|---|---|---|---|---|
| Tascioglu et al. (2012)[15] (1.5 J/point) & (3.0 J/point) | carpal tunnel syndrome | 60 | 14 males / 46 females | 40 / 20 | LLLT 1.5 J vs. LLLT 3.0 J vs. placebo LLLT | VAS for pain, SSS symptom severity scale, FSS functional status scale, grip strength, Nerve conduction studies, Ultrasonography evaluation | 7/10 | No |
| Vallone et al. (2014)[9] | Nonspecific chronic low back pain | 100 | 43 males / 57 females | 50 / 50 | LLLT & exercise vs. Exercise | VAS for pain | 5/10 | No |
| Yeldan et al. (2009)[28] | subacromial impingement | 60 | 13 males / 47 females | 34 / 26 | LLLT & cold-pack & exercise vs. placebo LLLT & cold-pack & exercise | VAS for pain, DASH questionnaire (Disabilities of the arm shoulder and hand), Shoulder Disability Questionnaire (SDQ), Dynamometry for muscle strength, ROM | 7/10 | No |

| Group by WALT | Study name | Difference in means | Standard error | Variance | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|---|---|
| no-WALT | Abrisham et al. (2011) | -0,900 | 0,177 | 0,031 | -1,246 | -0,554 | -5,091 | 0,000 |
| no-WALT | Al Rashoud et al. (2013) | -0,600 | 0,632 | 0,400 | -1,839 | 0,639 | -0,949 | 0,343 |
| no-WALT | Alfredo et al. (2012) | -0,210 | 0,953 | 0,908 | -2,077 | 1,657 | -0,220 | 0,826 |
| no-WALT | Ay et al. (2010 acute) | 0,700 | 0,453 | 0,205 | -0,187 | 1,587 | 1,547 | 0,122 |
| no-WALT | Ay et al. (2010 chronic) | 0,000 | 0,455 | 0,207 | -0,893 | 0,893 | 0,000 | 1,000 |
| no-WALT | Dogan et al. (2010) | -0,870 | 0,492 | 0,242 | -1,834 | 0,094 | -1,768 | 0,077 |
| no-WALT | Jiang et al. (2011 mild CTS) | -2,260 | 0,327 | 0,107 | -2,900 | -1,620 | -6,921 | 0,000 |
| no-WALT | Jiang et al. (2011 moderate CTS) | -1,160 | 0,515 | 0,265 | -2,170 | -0,150 | -2,252 | 0,024 |
| no-WALT | Kheshie et al. (2014) | -0,960 | 0,275 | 0,075 | -1,498 | -0,422 | -3,494 | 0,000 |
| no-WALT | Meireles et al. (2010) | 0,990 | 0,602 | 0,363 | -0,191 | 2,171 | 1,644 | 0,100 |
| no-WALT | Santos et al. (2012) | -1,000 | 0,585 | 0,342 | -2,147 | 0,147 | -1,709 | 0,087 |
| no-WALT | Tascioglu et al. (2012 - 1.5J/point) | -0,750 | 0,589 | 0,347 | -1,905 | 0,405 | -1,273 | 0,203 |
| no-WALT | Tascioglu et al. (2012 - 3J/point) | -0,500 | 0,725 | 0,525 | -1,920 | 0,920 | -0,690 | 0,490 |
| no-WALT | Vallone et al. (2014) | -1,400 | 0,276 | 0,076 | -1,940 | -0,860 | -5,080 | 0,000 |
| no-WALT | Yeldan et al. (2009) | -0,050 | 0,503 | 0,253 | -1,035 | 0,935 | -0,099 | 0,921 |
| no-WALT | | -0,680 | 0,210 | 0,044 | -1,091 | -0,268 | -3,235 | 0,001 |
| WALT | Emanet et al. (2010) | -0,850 | 0,367 | 0,135 | -1,569 | -0,131 | -2,317 | 0,021 |
| WALT | Fusakul et al. (2014) | -0,330 | 1,301 | 1,693 | -2,880 | 2,220 | -0,254 | 0,800 |
| WALT | Kiritsi et al. (2010) | -2,200 | 0,874 | 0,764 | -3,913 | -0,487 | -2,517 | 0,012 |
| WALT | Konstantinovic et al. (2010a) | -0,610 | 0,257 | 0,066 | -1,113 | -0,107 | -2,375 | 0,018 |
| WALT | Konstantinovic et al. (2010b) | -1,428 | 0,067 | 0,004 | -1,558 | -1,298 | -21,454 | 0,000 |
| WALT | Malliaropoulos et al. (2013) | -3,181 | 0,252 | 0,064 | -3,675 | -2,687 | -12,617 | 0,000 |
| WALT | | -1,520 | 0,417 | 0,174 | -2,338 | -0,702 | -3,642 | 0,000 |
| Overall | | -0,850 | 0,188 | 0,035 | -1,217 | -0,482 | -4,527 | 0,000 |




Identification
Screening
Eligibility
Included
Records identified through data-base MEDLINE (PubMed) and PEDro (Physiotherapy Evidence Database) searching (n = 124)
Additional records suggested by experts (n = 3)
Potentially relevant articles identified after duplicates removed (n = 94)
Relevant articles retrieved for more detailed analysis screened (n = 94)
Irrelevant articles excluded (n = 75)
Full-text articles assessed for eligibility (n = 19)
Full-text articles excluded, for reasons of low methodological quality (n=1)
Studies included in qualitative synthesis (n = 18)
Studies included in quantitative synthesis (meta-analysis) (n = 18)



Funnel Plot of Standard Error by Difference in means
Standard Error
0.0
0.5
1.0
1.5
2.0
-4
-3
-2
-1
0
1
2
3
4
Difference in means