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Low-level laser therapy for carpal tunnel syndrome (Review)

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[Intervention Review]

Low-level laser therapy for carpal tunnel syndrome

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ABSTRACT

Background

The role of low-level laser therapy (LLLT) in the management of carpal tunnel syndrome (CTS) is controversial. While some trials have shown distinct advantages of LLLT over placebo and some other non-surgical treatments, other trials have not.

Objectives

To assess the benefits and harms of LLLT versus placebo and versus other non-surgical interventions in the management of CTS.

Search methods

On 9 December 2016 we searched CENTRAL, MEDLINE, Embase, and Science Citation Index Expanded for randomised controlled trials (RCTs). We also searched clinical trial registries for ongoing studies. We checked the references of primary studies and review articles, and contacted trial authors for additional studies.

Selection criteria

We considered for inclusion RCTs (irrespective of blinding, publication status or language) comparing LLLT versus placebo or non-surgical treatment for the management of CTS.

Data collection and analysis

Two review authors independently identified trials for inclusion and extracted the data. For continuous outcomes, we calculated the mean difference (MD) or standardised mean difference (SMD) with a 95% confidence interval (CI) using the random-effects model, calculated using Review Manager. For dichotomous data, we reported risk ratio (RR) and 95% CI.

Main results

We identified 22 trials randomising 1153 participants that were eligible for inclusion; nine trials (525 participants, 256 randomised to LLLT) compared LLLT with placebo, two (150 participants, 75 randomised to LLLT) compared LLLT with ultrasound, one compared LLLT with placebo and LLLT with ultrasound, two compared LLLT with steroid injection, and one trial each compared LLLT with other non-surgical interventions: fascial manipulation, application of a pulsed magnetic field, transcutaneous electrical nerve stimulation (TENS), steroid injection, tendon gliding exercises, and applying a wrist splint combined with non-steroidal anti-inflammatory drugs. Three studies compared LLLT as part of multiple interventions. Risk of bias varied across the studies, but was high or unclear in most assessed domains in most studies. Most studies were small, with few events, and effect estimates were generally imprecise and

inconsistent; the combination of these factors led us to categorise the quality of evidence for most outcomes as very low or, for a small number, low.

At short-term follow-up (less than three months), there was very low-quality evidence for any effect over placebo of LLLT on CTS for the primary outcome of Symptom Severity Score (scale 1 to 5, higher score represents worsening; MD -0.36, 95% CI -0.78 to 0.06) or Functional Status Scale (scale 1 to 5, higher score represents worsened disability; MD -0.56, 95% CI -1.03 to -0.09). At short-term (less than three months) follow-up, we are uncertain whether LLLT results in a greater improvement than placebo in visual analogue score (VAS) pain (scale 0 to 10, higher score represents worsening; MD -1.47, 95% CI -2.36 to -0.58) and several aspects of nerve conduction studies (motor nerve latency: higher score represents worsening; MD -0.09 ms, 95% CI -0.16 to -0.03; range 3.1 ms to 4.99 ms; sensory nerve latency: MD -0.10 ms, 95% CI -0.15 to -0.06; range 1.8 ms to 3.9 ms), as the quality of the evidence was very low. When compared with placebo at short-term follow-up, LLLT may slightly improve grip strength (MD 2.58 kg, 95% CI 1.22 to 3.95; range 14.2 kg to 25.23 kg) and finger-pinch strength (MD 0.94 kg, 95% CI 0.43 to 1.44; range 4.35 kg to 5.7 kg); however, the quality of evidence was low. Only VAS pain and finger-pinch strength results reached the minimal clinically important difference (MCID) as previously published.

We are uncertain about the effect of LLLT in comparison to ultrasound at short-term follow-up for improvement in VAS pain (MD 2.81, 95% CI 1.21 to 4.40) and motor nerve latency (MD 0.61 ms, 95% CI 0.27 to 0.95), as the quality of evidence was very low. When compared with ultrasound at short-term follow-up, LLLT may result in slightly less improvement in finger-pinch strength (MD -0.71 kg, 95% CI -0.94 to -0.49) and motor nerve amplitude (MD -1.90 mV, 95% CI -3.63 to -0.18; range 7.10 mV to 9.70 mV); however, the quality of evidence was low.

There was insufficient evidence to assess the long-term benefits of LLLT versus placebo or ultrasound. There was insufficient evidence to show whether LLLT is better or worse in the management of CTS than other non-surgical interventions. For all outcomes reported within these other comparisons, the quality of evidence was very low.

There was insufficient evidence to assess adverse events, as only one study reported this outcome.

Authors' conclusions

The evidence is of very low quality and we found no data to support any clinical effect of LLLT in treating CTS. Only VAS pain and finger-pinch strength met previously published MCIDs but these are likely to be overestimates of effect given the small studies and significant risk of bias. There is low or very low-quality evidence to suggest that LLLT is less effective than ultrasound in the management of CTS based on short-term, clinically significant improvements in pain and finger-pinch strength.

There is insufficient evidence to support LLLT being better or worse than any other type of non-surgical treatment in the management of CTS. Any further research of LLLT should be definitive, blinded, and of high quality.

PLAIN LANGUAGE SUMMARY

Laser therapy for carpal tunnel syndrome

Review question

What are the effects of low-level laser therapy (LLLT) for the treatment of carpal tunnel syndrome (CTS) when compared to inactive treatment or other non-surgical treatments? What are the short-term and long-term benefits? Are there any harmful effects?

Background

CTS is a condition where one of the main nerves in the wrist is compressed. The underlying cause is often unknown. CTS can cause pain, tingling, and numbness in the hand. It is more common as we age and women are more often affected than men. CTS can be treated with surgery, but this is not without risk. For people who do not wish to have surgery, or have a long wait until their operation, other treatments are available. LLLT is one of the non-surgical treatments available to manage CTS. Use of LLLT is controversial, as some research has shown it to be of benefit whereas other research has not.

Search date

The evidence is current to December 2016.

Study characteristics

We collected and analysed all relevant studies to answer the review question. We found 22 clinical trials that assessed the safety and benefit of LLLT when compared to a placebo (pretend treatment) or another non-surgical treatment for CTS. Non-surgical treatments included ultrasound (delivery of sound waves to relieve pain), fascial manipulation (massage of deep connective tissue), application of a pulsed magnetic field, transcutaneous electrical nerve stimulation (TENS; delivery of electrical current through skin to nerves), steroid injection, tendon gliding exercises (to improve the movement of the nerve), and applying a wrist splint combined with non-steroidal anti-inflammatory drugs (pain killers that reduce inflammation). The trials involved 1153 participants. Most of these studies had weaknesses that could have compromised their results and caused them to overestimate or underestimate benefits or harms.

Quality of the evidence

We assessed the quality of the evidence as low quality or very low quality, due to poorly conducted studies, issues with study designs including lack of blinding (participants or assessor may have known which treatment was given and thereby anticipated the results), dissimilar results across studies, and not enough participants and therefore data.

Key results

We are uncertain whether LLLT improves symptoms of CTS more than placebo in the short term as the quality of the evidence is very low. Similarly, we are uncertain whether LLLT is less effective than ultrasound treatment in the short term as the quality of evidence Is very low. We do not know whether LLLT is better or worse than any other non-surgical treatment as evidence is lacking. There is also not enough evidence to draw any conclusions about any long-term benefits or harms of LLLT. There is not enough evidence to draw any conclusions about the adverse events a participant may experience from using LLLT. We need more well-designed, well-conducted research to find out how effective and safe LLLT is in the management of CTS.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Low-level laser therapy compared to placebo for carpal tunnel syndrome

Patient or population: carpal tunnel syndrome
Setting:
Intervention: low-level laser therapy
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with low-level laser therapy				
Overall improvement in CTS: SSS: short term (< 3 months) Scale from: 1 to 5	The mean overall improvement (as measured by SSS) short term (< 3 months) was 2.03	MD 0.36 lower (0.78 lower to 0.06 higher)	-	327 (7 RCTs)	⊕◯◯◯ Very low [1,2,3,4]	-
Overall improvement in CTS: SSS: long term Scale from: 1 to 5 Follow-up: mean 12 months	The mean overall improvement (as measured by SSS) long term was 2	MD 0.2 higher (0.54 lower to 0.94 higher)	-	25 (1 RCT)	⊕◯◯◯ Very low [1,3,4,5]	-
Overall improvement in CTS: FSS: short term (< 3 months) Scale from: 1 to 5	The mean FSS short term (< 3 months) was 2.16	MD 0.56 lower (1.03 lower to 0.09 higher)	-	159 (5 RCTs)	⊕◯◯◯ Very low [1,2,3,4]	-
Overall improvement in CTS: FSS: long term Scale from: 1 to 5 Follow-up: mean 12 months	The mean FSS long term was 2.3	MD 0.1 lower (0.73 lower to 0.53 higher)	-	25 (1 RCT)	⊕◯◯◯ Very low [1,3,4,5]	-

Adverse events	-	-	-	-	-	No adverse events reported in any trial.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **CTS:** carpel tunnel syndrome; **FSS:** Functional Status Scale; **MD:** men difference; **RCT:** randomised controlled trial; **SSS:** Symptom Severity Score.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] High risk of bias.
[2] Little overlap of confidence intervals and heterogeneity in magnitude of effect.
[3] Total sample size under 400 in total in both groups.
[4] Because of the few trials, we were unable to assess publication bias by funnel plot.
[5] Only one trial.

BACKGROUND

Description of the condition

Carpal tunnel syndrome (CTS) is a neuromuscular condition in which the median nerve becomes compressed at the level of the wrist secondary to increased pressure within the carpal tunnel (Keith 2009; Kerwin 1996). Disease processes or injury that increase the volume of the contents of the tunnel, including tumour, inflammation, oedema, and obesity, will elevate the pressure within the carpal tunnel. Conditions that reduce the volume of the tunnel (e.g. rheumatoid arthritis or previous fracture) can also predispose to CTS. Any disease that predisposes to peripheral neuropathy (damage to the nerves) can render the median nerve more susceptible to CTS. The cause is most commonly idiopathic (unknown), but a number of conditions are associated with CTS including pregnancy, untreated hypothyroidism, acromegaly, mucopolysaccharidosis, diabetes, amyloidosis, space-occupying lesions in the tunnel, and obesity. Many other associations have been suggested (Kerwin 1996).

The symptoms of CTS include pain and paraesthesia (abnormal sensation, typically tingling) in the sensory distribution of the median nerve in the wrist and hand (the thumb, index, and middle fingers, and radial half of the ring finger) (Rempel 1998; Szabo 1994). Wasting of the thenar (thumb) muscles can occur in advanced cases (Szabo 1994). CTS is the most common type of entrapment neuropathy (a disease process caused by direct pressure on a single nerve - in this case, the median nerve), with a prevalence of 3.8% for clinically diagnosed cases and 2.7% for electrophysiologically confirmed cases, when measured across a sample of 170,000 of the general population in Sweden (Atroshi 1999). Women are more commonly affected than men and its incidence increases with age: women between the ages of 40 and 60 years experience CTS four times more commonly than men (Atroshi 1999). The most commonly used diagnostic test is nerve conduction studies (NCS). This demonstrates slowing of median nerve conduction and, in severe cases, evidence of axonal loss at the carpal tunnel. NCS are considered the most reliable available, though not perfect, diagnostic test. Median sensory and motor NCS are valid and reproducible clinical laboratory studies that confirm a clinical diagnosis of CTS with a high degree of sensitivity and specificity (Jablecki 1993).

CTS can be treated using surgical or non-surgical interventions. Surgical interventions are usually offered to people who have persistent CTS symptoms, severe sensory disturbance, or thenar muscle wasting (AAN 1993). Non-surgical interventions can be offered to people who experience intermittent symptoms of mild to moderate CTS or to people who do not wish to have surgery, or as a temporary measure for people awaiting surgery (Atroshi 1999; De Krom 1992). Cochrane Reviews on CTS have concluded the benefit of surgical interventions (Scholten 2007 (part update in Vasiliadis 2014); Verdugo 2008), steroid injections (Marshall 2007), and splints (Page 2012a). Many other non-surgical interventions have been suggested, for most of which there are insufficient high-quality studies for a conclusion to be drawn on efficacy.

Description of the intervention

LLLT is the application of red and near infrared light, typically in the 600 nm to 1000 nm wavelength spectrum, to biological tissues to achieve therapeutic outcomes. It emits no heat, sound, or vibration. Instead of producing a thermal effect, LLLT may act by non-thermal or photochemical reactions in cells. It can be produced by laser or high-intensity light-emitting diodes, which are placed against the skin of the painful area. LLLT devices typically deliver a power density in the ranges from 10 mW to 500 mW (Bjordal 2003).

There is a lack of reports of adverse events in relation to LLLT (Chung 2012). Temporary discomfort at the application site has been reported (Fusakul 2014). A hypothesised potential adverse effect includes stimulating proliferation of existing skin cancer cells (Frigo 2009).

Description of the comparators in this review

Splinting involves immobilisation of the wrist in a neutral position (where the wrist is in straight alignment with the forearm: no flexion (palm toward wrist), extension (back of hand raised), radial or ulnar deviation (twisting)) for a specified period of time. Pressure on the carpal tunnel is increased in positions of wrist flexion and extension. With the wrist held in a neutral position, pressure on the carpal tunnel is reduced, which can lead to an improvement in symptoms (Gelberman 1984). One Cochrane systematic review concluded that there is limited evidence that a splint worn at night is more effective than no treatment in the short term (Page 2012a). However, the authors noted a lack of participant blinding and unclear allocation concealment within studies and suggested interpretation of the findings with caution. There was insufficient evidence regarding the effectiveness and safety of one splint design or wearing regimen over others, and of splint over other non-surgical interventions for CTS.

Non-steroidal anti-inflammatory drugs (NSAIDs) work by inhibiting an enzyme called cyclo-oxygenase, which is involved in the production of prostaglandins that contribute to the production of inflammation and pain. Reduction of these prostaglandins can help relieve symptoms related to inflammation and mild to moderate pain (Labelle 1997).

Therapeutic ultrasound involves delivering sound waves, via application of a round-headed instrument to the skin of the painful area, that are absorbed by the underlying tissues to help relieve pain and lessen disability. Its exact mechanism of action is contested. Early experimental work suggested a thermal anti-inflammatory and tissue-stimulating effect (Hong 1988). Newer research suggests that it does not have an anti-inflammatory effect but accel-

erates the process of resolution of oedema within the carpal tunnel, with subsequent reduction in carpal tunnel pressures (Yildiz 2011). One Cochrane systematic review concluded that there was only poor-quality evidence from very limited data to suggest that ultrasound may be more effective than placebo for either short-term or long-term symptom improvement in people with CTS (Page 2013). When examining its effects compared to other non-surgical interventions, such as splinting or laser therapy, the review concluded that there is insufficient evidence to support the use of ultrasound as a treatment with greater efficacy when compared to other non-surgical interventions for CTS. The review examined one trial looking at ultrasound versus laser therapy (Bakhtiary 2004), and one trial comparing ultrasound in conjunction with applying a wrist splint to laser therapy with applying a wrist splint (Dincer 2009).

Transcutaneous electrical nerve stimulation (TENS) delivers electrical stimulation to the underlying peripheral nerves via electrodes placed over the intact skin surface. This electrical stimulation to primary sensory afferent fibres activates inhibitory interneurons, blocking the transmission of pain signals from nociceptive pain fibres. This action serves to dampen the perception of pain (Sluka 2003).

Corticosteroid injections are administered within the carpal tunnel to provide symptomatic improvement. The mechanism of action is poorly understood. One Cochrane systematic review concluded that local corticosteroid injection provides greater clinical improvement in symptoms one month after injection compared to placebo; relief beyond one month was not demonstrated (Marshall 2007). The review also included comparisons of steroid injection to other non-surgical interventions. This included one trial comparing steroid injection to laser therapy, which showed steroid injection did not improve clinical outcome compared to laser therapy at six months (Lucantoni 1992).

Fascial manipulation is a manual therapy that focuses on massage of deep muscular fascia. The intervention is hypothesised to stretch surrounding fascia to reduce pressure on the median nerve within the carpal tunnel and therefore provide symptomatic relief (Pratelli 2015).

Tendon-gliding exercises involve taking the median nerve through its available range of motion in an attempt to improve the excursion of the nerve, reducing symptoms by decreasing adhesions, facilitating venous return, and facilitating dispersal of oedema in the carpal tunnel (Atya 2011). One Cochrane systematic review examined the efficacy of mobilisation interventions, including tendon gliding exercises (TGE) (Page 2012b). The review concluded that there is limited and very low-quality evidence of benefit for mobilisation interventions for CTS and that the use of this type of non-surgical intervention should be based on the clinician's expertise in being able to deliver these treatments and patient preferences.

Pulsed magnetic field (PMF) therapy is based on the principle of an interaction between non-ionising electromagnetic fields and biological systems to relieve pain. It is hypothesised that treatment effects may be related to increased local cellular activity, orientation of collagen fibres, and vasodilation of blood vessels (Quittan 2000).

How the intervention might work

LLLT is applied with the aim of reducing inflammation and providing symptomatic relief for acute and chronic pain. It is thought to produce an analgesic effect by lowering levels of pain mediators such as prostaglandins, beta-endorphins, interleukin 1-beta and tumour necrosis factor-alpha, as well as by improving local microcirculation (Bingol 2005; Brosseau 2005; Jablecki 1993).

The biochemical mechanisms underlying the therapeutic effects of LLLT are not well-established (Chung 2012). It is suggested that infrared light is absorbed by cellular chromophores on mitochondria (Greco 1989) to increase adenosine triphosphate (ATP) production (Karu 1999), with resultant modulation of reactive oxygen species and induction of transcription factors (Chen 2011). Several transcription factors are indicated: redox factor-1, dependent activator protein-1, nuclear factor kappa B, p53, activating transcription factor/cAMP-response element-binding protein, hypoxia-inducible factor, and hypoxia-inducible factor (HIF)-like factor (Chen 2011). The downstream effects of the protein synthesis following activation of these transcription factors are hypothesised to include increased cell proliferation and migration; modulation in the levels of cytokines, growth factors, and inflammatory mediators; and increased tissue oxygenation (Karu 2005).

Why it is important to do this review

Surgical treatment options for people with CTS have been examined in other Cochrane Reviews: Surgical treatment options for CTS (Scholten 2007), and the effect of surgical versus non-surgical treatment (Verdugo 2008). Cochrane systematic reviews of local steroid injection (Marshall 2007), splinting (Page 2012a), therapeutic ultrasound (Page 2013), mobilisation interventions (Page 2012b), and ergonomic interventions (O'Connor 2012) for CTS already exist, and up-to-date Cochrane systematic reviews of other non-surgical interventions for CTS are required.

A number of placebo-controlled studies have reported that LLLT can alleviate clinical symptoms and improve electrophysiological parameters (as measured in NCS) in people with CTS (Chang 2008; Evcik 2007; Shooshtari 2008; Naeser 2002), while other studies have not found a difference between LLLT and placebo (Irvine 2004; Tascioglu 2012). LLLT has been studied as a treatment in other painful conditions. One Cochrane systematic review investigating the use of LLLT as a treatment in rheumatoid arthritis concluded that LLLT could be considered for short-term treatment for relief of pain and morning stiffness for people with rheumatoid arthritis (Brosseau 2005). However, a further review for its use in low back pain concluded that evidence was insuffi-

cient to either support or refute its effectiveness (Yousefi-Nooraie 2008).

This systematic review and meta-analysis of randomised controlled trials (RCTs) aimed to address whether LLLT is of benefit in the non-surgical treatment of people with CTS. We aimed to assess the effectiveness and safety of LLLT compared with placebo or other non-surgical modalities, namely splinting, therapeutic ultrasound, and corticosteroid injection. More specifically, we aimed to evaluate the relative impact of LLLT in relieving symptoms, producing functional recovery (return to work and daily activities), and assessing adverse events compared to other treatments.

OBJECTIVES

To qualitatively and quantitatively assess the clinical efficacy and safety of LLLT, when compared to placebo or other non-surgical treatment, in the management of CTS.

METHODS

Criteria for considering studies for this review

Types of studies

We conducted this systematic review and meta-analysis in accordance with the PRISMA reporting guidelines for the conduct of meta-analysis of interventional trials (Liberati 2009). We submitted a prospective systematic review and meta-analysis protocol to PROSPERO (www.crd.york.ac.uk/PROSPERO; registration number: CRD42016037433) prior to commencement (Rankin 2016).

We included all RCTs or quasi-RCTs that compared LLLT with placebo or any non-surgical intervention, irrespective of language, blinding, publication status, sample size, or whether the trials were adequately powered.

Types of participants

People with a diagnosis of CTS, as defined by the authors of each study; we excluded people with a history of previous surgery for CTS. There were no restrictions placed on the use of LLLT while awaiting surgery or as a standalone treatment.

Types of interventions

All LLLT interventions (with differing wavelength, intensity, and duration) versus placebo or non-surgical treatments were included. All non-surgical treatments (regardless of dose, duration, etc.) were eligible for inclusion. We excluded trials that assessed the effects of LLLT in combination with another intervention, which was compared to a different intervention or the additional intervention without placebo LLLT (so the additional effect of LLLT could not be determined). We excluded trials comparing LLLT to surgical treatment.

Types of outcome measures

Primary outcomes

- Overall improvement in CTS, as measured by the patient-reported Symptom Severity Score (SSS) and Functional Status Scale (FSS) (Levine 1993). An increase in SSS or FSS represents increased severity of symptoms or worsened disability.

Secondary outcomes

- Visual analogue score (VAS) pain (McCormack 1988). An increase in VAS pain represents increased severity of pain.
- Strength measured by dynamometry (grip strength and finger-pinch strength).
- Nerve conduction studies (NCS). An increase in amplitude or velocity, or a decrease in latency, represents an improvement in nerve conduction.
- Adverse events, defined as the number of participants with at least one adverse event, or serious adverse events, defined as the number of participants with at least one serious adverse event. We will distinguish adverse and serious adverse events in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice definitions.
- Any other measure of improvement in symptoms or function (e.g. Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire (Hudak 1996), overall improvement questionnaires, health-related quality of life, or time to return to work/resume activities of daily living).

For all outcomes, we considered both short-term effects (three months or less) and long-term effects (greater than three months). If multiple time points were reported, we considered the latest measurement within three months as 'short-term'. We considered the longest follow-up available, if greater than three months, as 'long-term'.

Search methods for identification of studies

Electronic searches

On 9 December 2016, we searched the following databases for eligible RCTs:

- Cochrane Register of Controlled Trials (CENTRAL; 2016, Issue 11);
- MEDLINE;
- Embase;
- Web of Science Core Collection

We searched the following databases for ongoing studies:

- US National Institutes for Health clinical trials registry (www.ClinicalTrials.gov);
- World Health Organization (WHO) International Clinical Trials Registry Platform (www.who.int/ictrp/en/).

We presented the search strategy for each database and clinical trial registries in Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6. We searched all databases from their inception to 9 December 2016. We imposed no restrictions on the language of publication.

Searching other resources

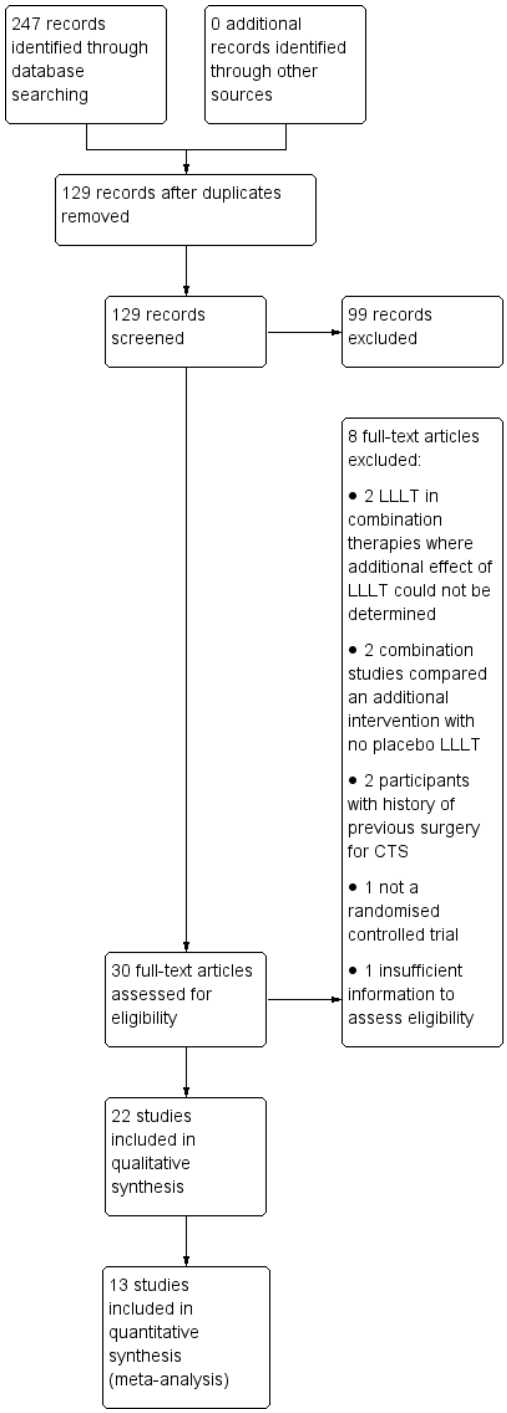
We searched the reference lists of all primary studies and review articles for additional references. We contacted trial authors to identify further studies. For included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed), we also searched for errata or retractions.

Data collection and analysis

Selection of studies

The review authors identified and excluded duplicate references. Two review authors (IR and HS) independently screened titles and abstracts of all studies identified by the search strategies and excluded studies that did not meet the inclusion criteria. They independently screened the full text of the study reports of the remaining studies. They identified studies for inclusion and recorded reasons for any exclusion of the ineligible studies in the Characteristics of excluded studies table. They resolved any disagreements through discussion and by consulting with a third review author (HR). We completed a PRISMA flow diagram (Figure 1).

Figure 1. Study flow diagram. LLLT: low-level laser therapy.



Data extraction and management

Two review authors (IR and HS) independently extracted study characteristics and outcome data from included studies using a standardised predesigned data extraction form. The data extraction form included information on setting, population, inclusion and exclusion criteria, interventions, comparison, and outcomes. We made notes on funding, baseline differences, and any notable conflicts of interest of trial authors. We resolved any disagreements through discussion or, if required, through consultation with a third review author (HR). We contacted trial authors when we required further information. One review author (IR) transferred the data into Review Manager 5 (RevMan 2014), and another review author (HS) checked the outcome data entries. We present details in the Characteristics of included studies table.

Assessment of risk of bias in included studies

Two review authors (IR and HS) independently assessed the risk of bias for each trial identifying the key trial reporting components using the CONSORT statement (Schulz 2011), and using the Cochrane 'Risk of bias' tool, described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed risk of bias based on information extracted from the reports of the included studies for the following: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of observers, incomplete outcome data, selective outcome reporting, and other sources of bias (e.g. inappropriate unit of analysis). We rated each item as at low, unclear, or high risk of bias. We summarised the 'Risk of bias' judgements across different studies for each of the domains listed. We resolved any discrepancies through discussion and by consulting with a third review author (HR). Table 8.5.c of the *Cochrane Handbook for Systematic Reviews of Interventions* details the criteria for judging the risk of bias in each study (Higgins 2011).

Measures of treatment effect

We used Review Manager 5 to perform data analysis (RevMan 2014). We pooled results of studies with similar characteristics (participants, interventions, outcome measures, and timing of outcome measures) to provide estimates of the efficacy of LLLT for CTS. We took the different interventions being compared into account in our data synthesis; for example, we analysed LLLT versus splinting studies separately from LLLT versus ultrasound studies. If a single study reported multiple trial arms, we included only the arms in which the interventions were LLLT and a comparator. When we could not combine data in the form of a meta-analysis, we presented a narrative synthesis of results. We expressed results for binary outcomes as risk ratios (RRs) with 95% confidence intervals (CIs). We expressed results for continuous outcomes (functional status, i.e. FSS; disability, i.e. DASH; grip strength; finger-pinch strength; NCS) as mean differences (MDs) with 95% CIs where the same scale was used, and as standardised mean differences (SMDs) with 95% CIs where different scales were used. Ordinal outcomes (questionnaires measuring overall improvement with ratings such as 'improved' or 'not improved') were treated and analysed as continuous outcomes. We planned to report the results of time-to-event outcomes (time to return to work and time to return to activities of daily living) using hazard ratios, but the included trials did not report these outcomes.

Unit of analysis issues

Where trialists had made inappropriate adjustments for bilateral involvement of wrists, we carried out a sensitivity analysis to account for a clustering unit-of-analysis error. Because results for wrists from the same person are not independent (i.e. they are likely to be correlated), an analysis that fails to take bilateral cases into account is likely to produce inappropriately narrow CIs.
In these circumstances (i.e. where studies included bilateral cases), we intended to adjust the summary effect estimate for each outcome for the intracluster correlation coefficient (ICC). As the ICC was not available from any included trial, we were unable to perform this adjustment. To assess for differences in the interpretation of effect estimate that may have occurred because of this unit-of-analysis error, we performed a sensitivity analysis utilising multiple different ICCs. These ranged from 0.01 to 1.00. These analyses are discussed at the relevant sections of the results. The presented 'Summary of findings' tables and forest plot analyses were unable to include adjustment for clustering effects from unit-of-analysis errors (as the correct ICC is unknown), and so presented original trial author data.

Dealing with missing data

We reported per-protocol analysis. We were unable to perform multiple imputation analysis to account for missing data due to postrandomisation dropouts because no authors reported this or presented individual participant data. We contacted trial authors for further information; however, this was not provided.

Assessment of heterogeneity

We assessed clinical heterogeneity by comparing the participants' characteristics and the methodology across studies. We assessed statistical heterogeneity using the Chi^2 test with significance set at P = 0.10 and measured the quantity of heterogeneity using the

I^2 statistic (Higgins 2002). We interpreted the I^2 statistic using the following ranges as an approximate guide: 0% to 40% might not be important heterogeneity, 30% to 60% might represent moderate heterogeneity, 50% to 90% might represent substantial heterogeneity, and 75% to 100% might represent considerable heterogeneity (Deeks 2011).

Assessment of reporting biases

For outcomes that included data from at least 10 studies, we intended to draw funnel plots to assess the association between study size and effect size. Where appropriate, we would also have used these funnel plots to distinguish between reporting bias and other causes of asymmetry (Peters 2008). However, sufficient studies were not available to conduct these analyses.

Data synthesis

We carried out meta-analyses of pooled results using a random-effects model, as this was more conservative than the fixed-effect model. We used the DerSimonian and Laird method in the meta-analysis of binary outcomes (DerSimonian 1986) and the inverse variance method for continuous outcomes.

'Summary of findings' tables

We included 'Summary of findings' tables for all comparisons for which data were available. We presented the following outcomes:

- Overall improvement (as measured by SSS) short term (less than three months);
- Overall improvement (as measured by SSS) long term;
- FSS short term (less than three months);
- FSS long term;
- Adverse events.

We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence (studies that contributed data for a prespecified outcome). We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We used GRADEpro GDT software (gradepro.org/). We provided footnotes to explain decisions to downgrade or upgrade the quality of evidence.

We did not produce a 'Summary of findings' table for comparisons if there were no data for any prespecified outcome.

Subgroup analysis and investigation of heterogeneity

We intended to perform subgroup analyses for sex, age, severity of CTS symptoms, and studies at high versus studies at low risk of bias. However, sufficient information was not available for these subgroup analyses.

Sensitivity analysis

As described under Unit of analysis issues, we performed sensitivity analyses utilising multiple different ICCs to assess for differences in interpretation of effect estimate. The ICCs ranged from 0.01 to 1.00. The findings are commented upon in each relevant section of the results.

We performed a fixed-effect analysis to investigate small-study effects.

RESULTS

Description of studies

Results of the search

We identified 247 references through electronic searches of CENTRAL (64 papers), MEDLINE (18 papers), Embase (90 papers), and Web of Science (75 papers). We excluded 118 duplicates and 99 irrelevant references through reading the abstracts. We retrieved 30 references for further assessment. We identified no further studies through scanning reference lists of the identified RCTs. We included 22 trials in the extraction of data for analysis (Aigner 1999; Atya 2011; Bakhtiary 2004; Casale 2013; Chang 2008; Dakowicz 2011; Dincer 2009; Ekim 2007; Evcik 2007; Fusakul 2014; Irvine 2004; Jiang 2011; Lazovic 2014; Lucantoni 1992; Pratelli 2015; Rayegani 2013; Rodrigues 2013; Saeed 2012; Shooshtari 2008; Soltani 2013; Tascioglu 2012; Tikiz 2013). We excluded eight studies for the reasons listed in the Characteristics of excluded studies table (Barbosa 2016; Branco 1999; Kotb 2014; Montes-Molina 2011; Naeser 2002; Padua 1999; Tamam 2012; Yagci 2009). The PRISMA flow diagram is shown in Figure 1.

Included studies

For each included trial, we collected details about the setting, population, inclusion and exclusion criteria, intervention, comparison, and outcomes (Characteristics of included studies table). All included trials were completed. Nine trials compared LLLT versus placebo, two compared LLLT versus ultrasound, one trial compared LLLT versus placebo and LLLT versus ultrasound, two compared LLLT versus steroid injection, and one each compared LLLT versus fascial manipulation, LLLT versus PMF, LLLT versus TENS, LLLT versus wrist splint with NSAIDs, and LLLT versus TGEs. Three trials measured LLLT as part of multiple interventions: one compared LLLT, applying a wrist splint, and vitamin B_6 versus placebo LLLT, applying a wrist splint, and vitamin B_6, one compared LLLT and applying a wrist splint versus placebo LLLT and applying a wrist splint, and one compared LLLT and applying a wrist splint versus ultrasound and applying a wrist splint. All

trials measured short-term outcomes. One trial measured long-term outcomes (at one year) for placebo and for ultrasound (Tikiz 2013), and one trial measured long-term outcomes (at six months) for steroid injection (Lucantoni 1992).

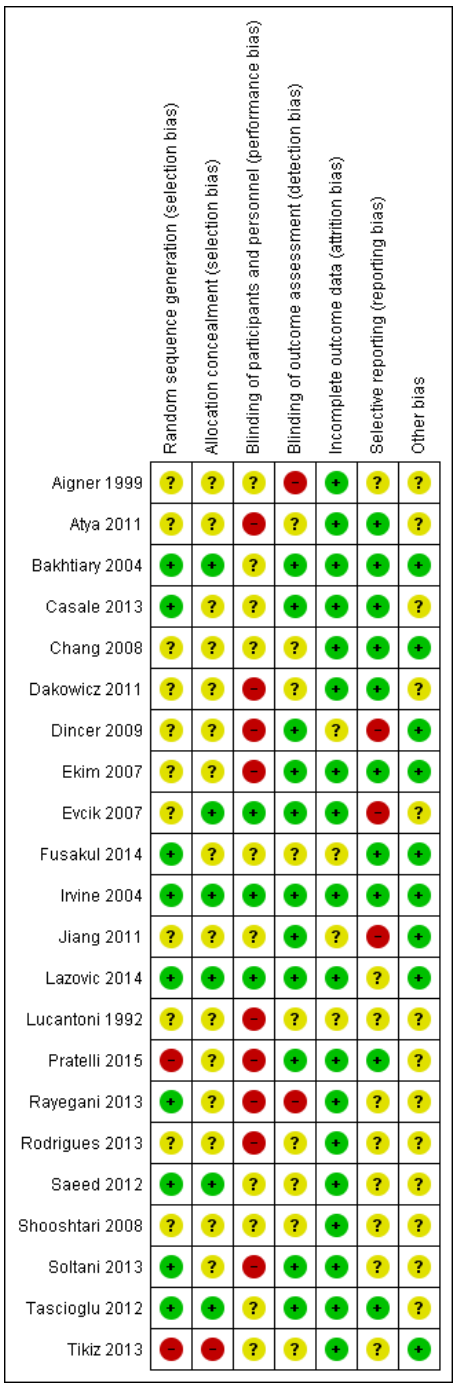
Excluded studies

The Characteristics of excluded studies table presents details about the reason for exclusion of the eight studies excluded after full-text review. Four studies used LLLT plus another intervention which was compared to the additional intervention without placebo or a different intervention for CTS (so the additional effect of LLLT could not be determined), two included participants with a history of previous surgery for CTS, one was not a RCT, and one had insufficient information to assess eligibility.

Risk of bias in included studies

The 'Risk of bias' summary figure (Figure 2) shows the risk of bias in included trials, and further information, including a quote or comment to support judgement, are available in the 'Risk of bias' tables within the Characteristics of included studies table. Risk of bias varied across the studies, but was generally high in most domains. All studies were small, ranging from 15 to 100 participants and therefore an overestimation of any effect was likely.

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Five trials reported an adequate method of random sequence generation with subsequent adequate allocation concealment. Only three LLLT versus placebo trials, and none of the LLLT versus ultrasound trials adequately reported the method of participant blinding. Six of the seven other non-surgical intervention studies were unblinded, and in the final trial the blinding methodology was unclear. Two of the combination trials did not have adequate blinding and the final trial was unclear. Lack of participant blinding may have influenced the self-reported outcomes of VAS pain, SSS, and FSS. Two trials did not perform blinding of outcome assessment, and a further nine trials were at unclear risk of bias. Attrition bias was unclear for four trials as there was insufficient information to assess whether the missing data mechanism was likely to have introduced bias in the estimate of effect and no methods were used to handle missing data, such as multiple imputation analysis. Some type of reporting bias was present in three studies and unclear in 10 studies. In particular, two trials appeared to be at risk of selective outcome reporting where the SSS was reported but not FSS - both are present within the same questionnaire (Evcik 2007; Jiang 2011). Unit-of-analysis errors occurred in seven trials that did not account for clustering due to inclusion of participants with bilateral wrists and separate units of allocations to each wrist (Bakhtiary 2004; Dincer 2009; Fusakul 2014; Lucantoni 1992; Pratelli 2015; Soltani 2013; Tikiz 2013).

Allocation

Five trials reported an adequate method of random sequence generation with subsequent adequate allocation concealment (Bakhtiary 2004; Irvine 2004; Lazovic 2014; Saeed 2012; Tascioglu 2012). One trial was at high risk of selection bias with inadequate random sequence generation and allocation concealment (Tikiz 2013), and one trial was at high risk of bias due to inadequate random sequence generation (Pratelli 2015). The remaining included trials were of unknown risk of bias from random sequence generation, allocation concealment, or both.

Blinding

Blinding of participants and personnel was at high risk of bias in nine studies (Atya 2011; Dakowicz 2011; Dincer 2009; Ekim 2007; Lucantoni 1992; Pratelli 2015; Rayegani 2013; Rodrigues 2013; Soltani 2013), as was blinding of outcome assessors in two studies (Aigner 1999; Rayegani 2013). There was low risk of bias in three studies where there was blinding of participants, personnel, and outcome assessors (Evcik 2007; Irvine 2004; Lazovic 2014). The remaining trials were of unknown risk of bias in one or both domains of blinding (of personnel and participants, or of outcome assessment).

Incomplete outcome data

Attrition bias was unclear for four trials as there was insufficient information to assess whether the missing data mechanism was likely to have introduced bias in the estimate of effect and the trialists did not use methods (such as multiple imputation analysis) to handle missing data (Dincer 2009; Fusakul 2014; Jiang 2011; Lucantoni 1992). The remaining trials were all at low risk of bias.

Selective reporting

Three studies were at high risk of reporting bias (Dincer 2009; Evcik 2007; Jiang 2011), and 9 were at unclear risk (Aigner 1999; Lazovic 2014; Lucantoni 1992; Rodrigues 2013; Rayegani 2013; Saeed 2012; Soltani 2013; Shooshtari 2008; Tikiz 2013). The remaining trials were at low risk of bias.

Other potential sources of bias

Nine trials were free of vested interest bias (Bakhtiary 2004; Chang 2008; Dincer 2009; Ekim 2007; Fusakul 2014; Irvine 2004; Jiang 2011; Lazovic 2014; Tikiz 2013). The remaining trials were at unclear risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Low-level laser therapy compared to placebo for carpal tunnel syndrome; **Summary of findings 2** Low-level laser therapy compared to ultrasound for carpal tunnel syndrome; **Summary of findings 3** Low-level laser therapy compared to fascial manipulation for carpal tunnel syndrome; **Summary of findings 4** Low-level laser therapy and a splint compared to ultrasound and a splint for carpal tunnel syndrome; **Summary of findings 5** Low-level laser therapy and a splint compared to placebo and a splint for carpal tunnel syndrome; **Summary of findings 6** Low-level laser therapy, wrist splint, and vitamin B_6 compared to placebo, wrist splint, and vitamin B_6 for carpal tunnel syndrome

Low-level laser therapy versus placebo

Ten randomised trials involving 550 participants (269 randomised to LLLT) compared LLLT with placebo (Aigner 1999; Chang 2008; Ekim 2007; Evcik 2007; Irvine 2004; Jiang 2011; Lazovic 2014; Shooshtari 2008; Tascioglu 2012; Tikiz 2013).

Study characteristics

Participants

All 10 trials included people with CTS as diagnosed by the study authors via clinical findings; five trials also required electrophysiological confirmation on NCS. In trials that reported age, the mean ranged from 46 to 54 years. The proportion of women where trials provided this demographic information ranged from 77% to 95%. One trial used wrists (including bilateral cases), not participants, as the unit of analysis and underwent subsequent sensitivity analysis (Tikiz 2013).

Interventions

The Characteristics of included studies table shows the types of LLLT used in each trial.

Risk of bias in included studies

We judged Irvine 2004 to be at low risk of bias and all other trials to be at unclear or high risk of bias. We found no protocols or trial registry entries for any study included in the review, so our assessment of selective reporting was limited to comparing outcomes reported in the methods and results sections of publications.

Primary outcomes

Overall improvement in carpal tunnel syndrome: Symptom Severity Score

An increase in SSS represents increased severity of symptoms. The scale ranges from 1 to 5, with an MCID of 1.14 (Kim 2013).
Seven trials involving 327 participants (176 randomised to LLLT) reported SSS in the short term (three months or less) (Chang2008; Ekim 2007; Evcik 2007; Irvine 2004; Jiang 2011; Tascioglu 2012; Tikiz 2013). Based on the meta-analysis of these seven trials, we observed no significant difference in SSS of participants treated with LLLT compared to placebo (MD -0.36, 95% CI -0.78 to 0.06; P = 0.09; Analysis 1.1). The GRADE quality of evidence was very low. See Summary of findings for the main comparison for details.
Tikiz 2013 involving 25 participants (13 randomised to LLLT) reported long-term (12-month) follow-up data for SSS. There was no significant difference between LLLT and placebo (MD 0.20, 95% CI -0.54 to 0.94; P = 0.6).

Overall improvement in carpal tunnel syndrome: Functional Status Scale

An increase in FSS represents worsened disability. The scale ranges from 1 to 5, with an MCID of 0.74 (Kim 2013).
Five trials involving 159 participants (90 randomised to LLLT) reported FSS (Chang 2008; Ekim 2007; Irvine 2004; Tascioglu 2012; Tikiz 2013). Based on the meta-analysis of these five trials, we observed a decrease in FSS scores of participants treated with LLLT compared to placebo (MD -0.56, CI -1.03 to -0.09; P = 0.02; Analysis 1.2). The GRADE quality of evidence was very low.
Tikiz 2013 involving 25 participants (13 randomised to LLLT) included long-term (12-month) follow-up data for FSS. There was no significant difference between LLLT and placebo (MD -0.10, CI -0.73 to 0.53; P = 0.76).

Secondary outcomes

Visual analogue score pain

An increase in VAS pain represents worsened pain. The scale ranges from 0 to 10, with an MCID of 1.2 (Kelly 2001).
Seven trials involving 392 participants (209 randomised to LLLT) reported short-term (three months or less) VAS pain (Chang 2008; Ekim 2007; Evcik 2007; Jiang 2011; Shooshtari 2008; Tascioglu 2012; Tikiz 2013). Based on the meta-analysis of these seven trials, we observed a significant decrease in VAS pain of participants treated with LLLT compared to placebo (MD -1.47, 95% CI -2.36 to -0.58; P = 0.001; Analysis 1.3). The GRADE quality of evidence was very low.
Lazovic 2014 reported VAS pain following conversion to an ordinal outcome: none (0), mild (greater than 0 to 4), moderate (greater than 4 to 7), and severe (greater than 7 to 10). This study found a significantly greater reduction in the level of pain following treatment in the LLLT group compared to the placebo group. A request was made to authors for original continuous data, however these were not provided and we were unable to include this trial in the meta-analysis. Tikiz 2013 included long-term (12-month) follow-up data for VAS pain. There was no significant difference between LLLT and placebo (MD -0.22, 95% CI -2.47 to 2.03; P = 0.85).

Strength measured by dynamometry: grip strength

Five trials involving 286 participants (154 randomised to LLLT) reported short-term (three months or less) grip strength (Chang 2008; Evcik 2007; Shooshtari 2008; Tascioglu 2012; Tikiz 2013). Based on the meta-analysis of these five trials, LLLT may increase grip strength compared to placebo (MD 2.58 kg, 95% CI 1.22 to 3.95; P = 0.0002; Analysis 1.4). The findings did not meet the MCID for grip strength, which has been reported as 2.69 kg in healthy people (Villafañe 2014). The GRADE quality of evidence was low.
Ekim 2007 measured grip strength; however, the paper did not state the units of measurement or type of dynamometer. There were no significant differences between LLLT and placebo groups. We were unable to obtain further information from the study authors and we were therefore unable to include data from this trial in the meta-analysis. Ekim 2007 reported no significant difference between LLLT and placebo for grip strength. As well as reporting short-term findings at three months, Tikiz 2013 reported long-

term (12-month) follow-up data for grip strength. There was no difference between LLLT and placebo (MD 3.6 kg, 95% CI -2.11 to 9.31; P = 0.22).

Strength measured by dynamometry: finger-pinch strength

Two trials involving 121 participants (61 randomised to LLLT) reported finger-pinch strength (Chang 2008; Evcik 2007). Based on the meta-analysis of these two trials, LLLT may increase finger-pinch strength compared to placebo (MD 0.94 kg, 95% CI 0.43 to 1.44; Analysis 1.5). The findings met the MCID for finger-pinch strength, which has been reported as 0.68 kg in healthy people (Villafañe 2014). The GRADE quality of evidence was low.

Nerve conduction studies

Seven trials involving 446 participants (236 randomised to LLLT) reported short-term (three months or less) findings of NCS (Chang 2008; Ekim 2007; Evcik 2007; Jiang 2011; Lazovic 2014; Shooshtari 2008; Tascioglu 2012). Tikiz 2013 reported long-term findings of NCS for LLLT but not for placebo LLLT. We requested further information from the study authors however this was not provided and we were unable to include this trial in the meta-analysis.

All seven trials reported motor nerve latency. Based on the meta-analysis of these seven trials, we observed a significant decrease in the motor nerve latency of participants treated with LLLT compared to placebo (MD -0.09 ms, 95% CI -0.16 to -0.03; P = 0.003; Analysis 1.6). The GRADE quality of evidence was very low.

Five trials involving 307 participants (156 randomised to LLLT) reported sensory nerve latency (Chang 2008; Ekim 2007; Evcik 2007; Jiang 2011; Shooshtari 2008). Based on the meta-analysis of these five trials, we observed a significant decrease in sensory nerve latency of participants treated with LLLT compared to placebo (MD -0.10 ms, 95% CI -0.15 to -0.06; P < 0.00001; Analysis 1.7). The GRADE quality of evidence was very low.

Two trials involving 139 participants (80 randomised to LLLT) reported sensory nerve velocity (Lazovic 2014; Tascioglu 2012). Based on the meta-analysis of these two trials, we observed no significant difference in sensory nerve velocity of participants treated with LLLT compared to placebo (MD 1.48 m/s, 95% CI -5.68 to 8.65; P = 0.68; Analysis 1.8). The GRADE quality of evidence was very low.

One trial reported sensory and motor amplitude (Evcik 2007). Evcik 2007 reported no significant difference between pretreatment and post-treatment mean scores for sensory amplitude in the LLLT group (pretreatment: 28.5 ± 13.4 μV; post-treatment: 29.6 ± 12.9 μV) or the placebo group (pretreatment: 27.6 ± 14.7 μV; post-treatment: 27.9 ± 13.4 μV). Comparing these two groups following treatment, we found no significant difference (MD 1.7 μV, 95% CI -4.03 to 7.43; P = 0.56). Evcik 2007 also reported no significant difference between pretreatment and post-treatment motor amplitude in the LLLT group (pretreatment: 6.8 ± 3.8 mV; post-treatment: 6.9 ± 3.4 mV) or the placebo group (pretreatment: 7.1 ± 3.3 mV; post-treatment: 7.2 ± 4.0 mV). Comparing these two groups following treatment, we found no significant differences (MD -0.30 mV, 95% CI -1.92 to 1.32; P = 0.72). The GRADE quality of evidence for all NCS outcomes was very low. The changes noted in NCS were minimal and did not represent a clinically important difference (Padua 1997).

Adverse events

This outcome was not reported in any trial.

Any other measure of improvement in symptoms or function

None of the trials reported any other measure of improvement in symptoms or function.

Variation in statistical analysis

The interpretation of the effect estimate did not change by adopting the random-effects or fixed-effect model. We chose the random-effects model as it is the more conservative of the effect models. The fixed-effect model did not change the direction of effect in any trial and did not change the direction or size of effect in trials with low heterogeneity (grip strength, finger-pinch strength).

Jiang 2011 reported change scores, all other trials reported final mean scores. Jiang 2011 reported two change scores, the initial change score was used (most significant change). Jiang 2011 reported CTS in two separate groups: mild and moderate, but combined them for analysis. Evcik 2007 and Chang 2008 reported total SSS and FSS, other trials reported mean SSS and FSS.

Subgroup analysis

We intended to carry out a subgroup analysis comparing trials at high and low risk of bias but this was not possible because only one trial was at low risk of bias (Irvine 2004). Irvine 2004 found no significant difference on any of the outcome measures (SSS and FSS) between LLLT and placebo.

Sensitivity analysis

Tikiz 2013 conducted their study and analysed results in terms of total number of wrists, not participants. To assess for differences in the interpretation of the effect estimate that may have occurred because of this unit-of-analysis error, we performed a sensitivity analysis utilising multiple different ICCs. These ranged from 0.01 to 1.00. The interpretation of the effect estimate did not change for any outcome during this analysis.

Low-level laser therapy versus ultrasound

Three randomised trials involving 177 participants (88 randomised to LLLT) compared LLLT to ultrasound (Bakhtiary 2004; Saeed 2012; Tikiz 2013).

Study characteristics

Participants

All trials included people with CTS as diagnosed by the study authors via clinical findings and NCS. The mean age in the trials that reported age ranged from 36 to 48 years. The proportion of females in the trials that provided this demographic information ranged from 55% to 88%. In two trials, the unit of analysis was wrists (including bilateral), not participants, and these trials underwent subsequent sensitivity analysis (Bakhtiary 2004; Tikiz 2013).

Interventions

The types of LLLT and ultrasound used in the trials are shown in the Characteristics of included studies table.

Risk of bias in included studies

The risk of bias in the included trials is summarised in the 'Risk of bias' summary figure (Figure 2). All studies were at unclear or high risk of bias. We found no protocols or trial registry entries for any of the studies included in the review, so our assessment of selective reporting was limited to comparing outcomes reported in the methods and results sections of publications.

Primary outcomes

Overall improvement in carpal tunnel syndrome: Symptom Severity Score

An increase in SSS represents increased severity of symptoms. The scale ranged from 1 to 5, with an MCID of 1.14.

Two trials involving 127 participants (63 randomised to LLLT) reported short-term (three months or less) SSS. Based on the meta-analysis of these two trials, SSS was higher (worse) with LLLT than ultrasound (MD 0.43, 95% CI 0.36 to 0.50; P = 0.00001; Analysis 2.1). The GRADE quality of evidence was very low. The findings did not meet the MCID of 1.14. See Summary of findings 2 for details.

Tikiz 2013 included long-term (12-month) follow-up data for SSS. There was no difference between LLLT and ultrasound (MD 0.20, 95% CI -0.55 to 0.95; P = 0.6).

Overall improvement in carpal tunnel syndrome: Functional Status Scale

An increase in FSS represents worsened disability. The scale ranged from 1 to 5, with an MCID of 0.74.

Two trials involving 127 participants (63 randomised to LLLT) reported short-term (three months or less) FSS (Saeed 2012; Tikiz 2013). Based on the meta-analysis of these two trials, FSS was higher (worse) with LLLT than ultrasound (MD 0.35, 95% CI 0.29 to 0.41; P < 0.0001; Analysis 2.2). The GRADE quality of evidence was very low. The findings did not meet the MCID of 0.74.

Tikiz 2013 included long-term (12-month) follow-up data for FSS. There was no significant difference between LLLT and ultrasound at 12 months (MD 0.00, 95% CI -0.75 to 0.75; P = 1.00).

Secondary outcomes

Visual analogue score pain

An increase in VAS pain represents worsened pain. The scale ranged from 0 to 10, with an MCID of 1.2.

Three trials involving 177 participants (88 randomised to LLLT) reported short-term (three months or less) VAS pain (Bakhtiary 2004; Saeed 2012; Tikiz 2013). Based on the meta-analysis of these three trials, VAS pain was higher (worse) with LLLT than ultrasound (MD 2.81, 95% CI 1.21 to 4.40; P < 0.0006; Analysis 2.3). The GRADE quality of evidence was very low. The difference met the MCID of 1.2.

Tikiz 2013 included long-term (12-month) follow-up data for VAS pain. At 12 months, there was no significant difference between LLLT and ultrasound (MD 1.48, 95% CI -0.56 to 3.52; P = 0.16).

Strength measured by dynamometry: grip strength

Two trials involving 77 participants (38 randomised to LLLT) reported grip strength (Bakhtiary 2004; Tikiz 2013). Bakhtiary 2004 reported values in Newtons (converted to kg for meta-analysis). Based on the meta-analysis of these two trials, we observed no difference in grip strength of participants treated with LLLT compared to ultrasound (MD -0.89 kg, 95% CI -4.30 to 2.52; P = 0.61; Analysis 2.4). The GRADE quality of evidence was very low.

Tikiz 2013 included long-term (12-month) follow-up data for grip strength. There was no significant difference between LLLT and ultrasound (MD 2.70, 95% CI -3.23 to 8.63; P = 0.37).

Strength measured by dynamometry: finger-pinch strength

One trial involving 50 participants (25 randomised to LLLT) reported finger-pinch strength (Bakhtiary 2004). Bakhtiary 2004

reported a change score for ultrasound as 9.9 ± 5.5 N and LLLT as 2.9 ± 1.5 N. Based on these results, the MD between the change scores was -7.00 N (95% CI -9.23 to -4.77; P < 0.001). The GRADE quality of evidence was low.

Nerve conduction studies

Three trials involving 177 participants (88 randomised to LLLT) reported findings for NCS (Bakhtiary 2004; Saeed 2012; Tikiz 2013). All three trials reported motor nerve latency. Based on the meta-analysis of these three trials, we observed a significant increase in motor latency of participants treated with LLLT compared to ultrasound (MD 0.61 ms, 95% CI 0.27 to 0.95; P = 0.004; Analysis 2.5). The GRADE quality of evidence was very low.

Tikiz 2013 included long-term (12-month) follow-up data for motor latency. There was no significant difference between LLLT and ultrasound (MD 0.10 ms, 95% CI -0.50 to 0.70; P = 0.75).

Three trials involving 177 participants (88 randomised to LLLT) reported sensory nerve latency (Bakhtiary 2004; Saeed 2012; Tikiz 2013). Based on the meta-analysis of these three trials, we observed no significant difference in sensory latency of participants treated with LLLT compared to ultrasound (MD -0.43 ms, 95% CI -0.01 to 0.87; P = 0.05; Analysis 2.6). The GRADE quality of evidence was very low.

Tikiz 2013 included long-term (12-month) follow-up data for sensory latency. There was no significant difference between LLLT and ultrasound (MD -0.20 ms, 95% CI -0.80 to 0.40; P = 0.52).

Two trials involving 77 participants (38 randomised to LLLT) reported motor amplitude. Based on the meta-analysis of these two trials, we observed a significant decrease in motor amplitude of participants treated with LLLT compared to ultrasound, favouring ultrasound (MD -1.90 mV, 95% CI -3.63 to -0.18; P = 0.03; Analysis 2.7). The GRADE quality of evidence was low.

Tikiz 2013 included long-term (12-month) follow-up data for motor amplitude. There was no significant difference between LLLT and ultrasound (MD 1.00 mV, 95% CI -2.11 to 4.11; P = 0.53).

Bakhtiary 2004 reported sensory amplitude. The study authors reported a significant increase in the sensory amplitude of ultrasound compared to LLLT (10.1 ± 6.9 μV with ultrasound compared to 4.4 ± 7.4 μV with LLLT). Based on these results, the MD between the change scores was -5.7 μV (95% CI -9.67 to -1.73; P = 0.005). The GRADE quality of evidence was very low.

Tikiz 2013 reported sensory velocity. The study authors reported no significant change for LLLT versus ultrasound at three months (MD 4.00 m/s, 95% CI -1.49 to 9.49; P = 0.15) or at 12 months (MD 2.90 m/s, 95% CI -2.02 to 7.82; P = 0.27). The GRADE quality of evidence was very low.

Adverse events

None of the trials reported this outcome.

Any other measure of improvement in symptoms or function

None of the trials reported any other measure of improvement in symptoms or function.

Variation in statistical analysis

We used a random-effects model for all outcomes as the more conservative model. We performed a fixed-effect model analysis to investigate the small-study effect: where a previous significant effect had been observed, there was no change in the interpretation of the effect estimate (VAS pain, motor latency, motor amplitude). A fixed-effect model produced a change in the effect estimate for SSS, FSS, grip strength, and sensory latency. Where previously there had been no significant difference, all produced significant differences. When a result is statistically significant using a fixed-effect model but not using a random-effects model, the cause is likely to be heterogeneity; we chose the random-effects model as it is the more conservative of the effect models.

Subgroup analysis

We deemed none of the trials at low risk of bias, so we did not perform a subgroup analysis.

Sensitivity analysis

Bakhtiary 2004 and Tikiz 2013 carried out their study and analysed their results in terms of total number of wrists, not participants. We performed a sensitivity analysis to account for a clustering unit-of-analysis error. The interpretation of the effect estimate changed for sensory latency to produce a significant difference with an ICC of 1.00, as a considerably higher weight was given to Saeed 2012 (see Analysis 2.8 (Figure 3) and Analysis 2.9 (Figure 4)). We chose the most conservative ICC for further discussion and conclusion; this did not change the interpretation of the effect estimate. The interpretation of the effect estimate did not change for any other outcomes during these analyses.

Figure 3. Sensory latency, pre-analysis.

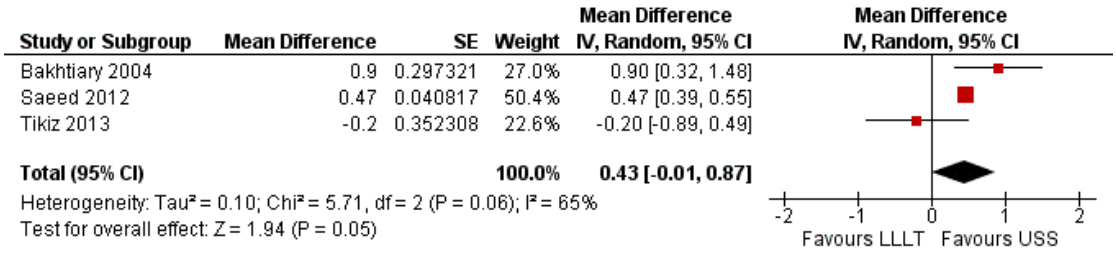
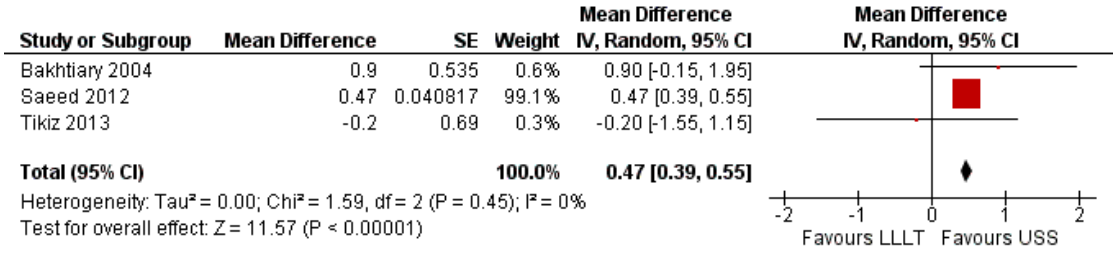


Figure 4. Sensory latency, intracluster correlation coefficient 1.00.



Low-level laser therapy versus fascial manipulation

One randomised trial involving 42 participants with 70 symptomatic hands (35 wrists randomised to LLLT, number of participants randomised to LLLT not stated) compared LLLT to fascial manipulation (Pratelli 2015).

Study characteristics

Participants

The trial included people with CTS as diagnosed by the study authors via clinical findings and NCS. The mean age of participants was 54 years and 69% were female. This trial analysed its unit of analysis as wrists (including bilateral), not participants, and underwent subsequent sensitivity analysis.

Interventions

The types of LLLT and fascial manipulation used in the trial are described in the Characteristics of included studies table.

Risk of bias in included studies

The trial was at high risk of bias. The risk of bias is summarised in the 'Risk of bias' summary figure (Figure 2).

Primary outcomes

Overall improvement in carpal tunnel syndrome: Symptom Severity Score

An increase in SSS represents increased severity of symptoms. The scale ranged from 1 to 5, with an MCID of 1.14.
The study authors reported a significant increase in SSS of LLLT versus fascial manipulation (MD 1.72, 95% CI 1.6 to 1.84). The GRADE quality of evidence was very low. The findings met the MCID. See Summary of findings 3 for details.

Overall improvement in carpal tunnel syndrome: Functional Status Scale

An increase in FSS represents worsened disability. The scale ranged from 1 to 5, with an MCID of 0.74.
The study authors reported a significant increase in FSS of LLLT versus fascial manipulation (MD 1.31, 95% CI 1.02 to 1.60). The

GRADE quality of evidence was very low. The findings met the MCID. See Summary of findings 3 for details.

Secondary outcomes

Visual analogue score pain

An increase in VAS pain represents worsened pain. The scale ranged from 0 to 10, with an MCID of 1.2.
The study authors reported a significant increase in VAS pain of LLLT versus fascial manipulation (MD 4.32, 95% CI 3.67 to 4.97). The GRADE quality of evidence was very low. The findings met the MCID.

Unreported outcomes

Study authors did not measure or report on the following outcomes: strength measured by dynamometry (grip strength and finger-pinch strength), NCS, adverse events, and any other measure of improvement in symptoms or function.

Sensitivity analysis

The unit of analysis was wrists, not participants. We performed a sensitivity analysis to account for a clustering unit-of-analysis error. The interpretation of the effect estimate did not change for any outcome during this analysis.

Low-level laser therapy versus pulsed magnetic field

One randomised trial involving 38 participants (18 randomised to LLLT) compared LLLT to PMF (Dakowicz 2011).

Study characteristics

Participants

The trial included people with CTS as diagnosed by the study authors via clinical findings and NCS. The mean age of participants was 51 years and 92% were female.

Interventions

The types of LLLT and PMF used in the trial are described in the Characteristics of included studies table.

Risk of bias in included studies

The trial was at high risk of bias. The risk of bias is summarised in the 'Risk of bias' summary figure (Figure 2).

Secondary outcomes

Visual analogue score pain

The study authors reported mean VAS pain values in a graph. They reported a significant reduction from baseline in both groups but did not report the significance of any difference when comparing the two groups. They did not report the measure of spread (e.g. standard deviation) and so we were unable to perform further analysis. We requested further information but none was provided.

Nerve conduction studies

The study authors reported that changes in sensory and motor latency were not significant, but did not present values.

Unreported outcomes

The study authors did not measure or report on the following outcomes: overall improvement in carpal tunnel syndrome: SSS, overall improvement in carpal tunnel syndrome: FSS, strength measured by dynamometry (grip strength and finger-pinch strength), adverse events, and any other measure of improvement in symptoms or function.

Low-level laser therapy versus transcutaneous electrical nerve stimulation

One randomised trial involving 20 participants (10 randomised to LLLT) compared LLLT to TENS (Casale 2013).

Study characteristics

Participants

The trial included people with CTS as diagnosed by the study authors via clinical findings and NCS. The mean age in the trial was 54 years and 69% of the participants were female.

Interventions

The types of LLLT and TENS used in the trial are described in the Characteristics of included studies table.

Risk of bias in included studies

The trial was at high risk of bias. This is summarised in the 'Risk of bias' summary figure (Figure 2).
We did not produce a 'Summary of findings' table for this comparisons as no data for any prespecified outcomes were available.

Secondary outcomes

Visual analogue score pain

An increase in VAS pain represents worsened pain. The scale ranged from 0 to 10, with an MCID of 1.2.
Analysis of the study authors' findings revealed a significant decrease in VAS pain of participants treated with LLLT compared to TENS (MD -1.20, 95% CI -2.27 to -0.13). The GRADE quality of evidence was very low.

Nerve conduction studies

Analysis of the authors' findings revealed a decrease in the motor latency of participants treated with LLLT compared to TENS (MD -0.70 ms, 95% CI -1.17 to -0.23) and an increase in the sensory nerve conduction velocity (MD 3.9 m/s, 95% CI 0.27 to 7.53). The GRADE quality of evidence for both outcomes was very low.

Unreported outcomes

The study authors did not measure or report on the following outcomes: overall improvement in carpal tunnel syndrome: SSS, overall improvement in carpal tunnel syndrome: FSS, strength measured by dynamometry (grip strength and finger-pinch strength), adverse events, and any other measure of improvement in symptoms or function.

Low-level laser therapy versus steroid injection

Two randomised trials involving 73 participants (36 randomised to LLLT) compared LLLT to steroid injection (Lucantoni 1992; Soltani 2013).

Study characteristics

Participants

Both trials included people with CTS as diagnosed by the study authors via clinical findings and NCS. The mean age in Lucantoni 1992 was not stated. The mean age in Soltani 2013 was 47 years. Across both trials, 93% of participants were female. Both trials analysed their unit of analysis as wrists (including bilateral), not participants, and underwent subsequent sensitivity analysis.

Interventions

The types of LLLT and steroid injection used in the trials are described in the Characteristics of included studies table.

Risk of bias in included studies

Both trials were at high risk of bias. This is summarised in the 'Risk of bias' summary figure (Figure 2).
We did not produce a 'Summary of findings' table for this comparison as there were no data for any prespecified outcome available.

Secondary outcomes

Visual analogue score pain

Analysis of the findings of Soltani 2013 revealed no significant difference in VAS pain of participants treated with LLLT compared to steroid injection (MD -0.50, 95% CI -1.80 to 0.80; P = 0.45).

Nerve conduction studies

Analysis of the findings of Lucantoni 1992 revealed no significant short-term difference in motor latency of participants treated with LLLT compared to steroid injection (MD -0.09 ms, 95% CI -0.58 to 0.40) or sensory nerve conduction velocity (MD -1.14 m/s, 95% CI -4.34 to 2.06). The GRADE quality of evidence of both outcomes was very low. Analysis of the study authors' findings revealed no significant long-term difference in motor latency of participants treated with LLLT compared to steroid injection (MD -0.48 ms, 95% CI -1.06 to 0.10) or sensory nerve conduction velocity (MD -0.75 m/s, 95% CI -4.31 to 2.81). The GRADE quality of evidence of both outcomes was very low.
Analysis of the findings of Soltani 2013 revealed no significant difference in motor latency of participants treated with LLLT compared to steroid injection (MD 0.00 ms, 95% CI -0.48 to 0.48) or sensory latency (MD -0.20 ms, 95% CI -0.51 to 0.11). The study authors reported no significant changes for sensory or motor amplitude but did not report the findings.
Both trials reported motor latency. Based on meta-analysis of these two trials, we observed no significant difference in motor latency of participants treated with LLLT compared to steroid injection (MD -0.04 ms, 95% CI -0.39 to 0.30; P = 0.80) (Analysis 3.1). The GRADE quality of evidence was very low.
Soltani 2013 also reported short-term outcomes for sensory latency, sensory amplitude, and motor amplitude. Analysis of their findings revealed no significant difference of participants treated with LLLT compared to steroid injection in sensory amplitude (MD -3.60 μV, 95% CI -7.34 to 0.14; P = 0.06), sensory latency (MD -0.10 ms, 95% CI -0.34 to 0.14; P = 0.42), or motor amplitude (MD -0.20 mV, 95% CI -0.61 to 0.21; P = 0.34). The GRADE quality of evidence of these outcomes was very low.

Any other measure of improvement in symptoms or function: symptom improvement questionnaires

Lucantoni 1992 reported a symptom improvement questionnaire: no improvement, slight improvement, moderate improvement,

disappearance of symptoms. We converted this to a 1 (disappearance) to 4 (no improvement) scale for analysis as a discontinuous ordinal outcome. Analysis of the findings of Lucantoni 1992 revealed less of an improvement in the short-term symptoms of participants treated with LLLT compared to steroid injection (MD 0.95, 95% CI 0.29 to 1.61; P = 0.005). The GRADE quality of evidence was very low.

Analysis of the findings of Lucantoni 1992 revealed no difference in the long-term (six months) symptoms of participants treated with LLLT compared to steroid injection (MD 0.20, 95% CI -0.46 to 0.86; P = 0.55). The GRADE quality of evidence was very low.

Unreported outcomes

The study authors did not measure or report on the following outcomes: overall improvement in carpal tunnel syndrome: SSS, overall improvement in carpal tunnel syndrome: FSS, strength measured by dynamometry (grip strength and finger-pinch strength), and adverse events.

Sensitivity analysis

The unit of analysis was not specified by the study authors in either of the trials. However, both contained participants who were treated for bilateral symptoms. To assess for units-of-analysis error, we performed a sensitivity analysis utilising multiple different ICCs to assess for differences in interpretation of effect estimate. The ICCs ranged from 0.01 to 1.00. The interpretation of the effect estimate did not change for any outcome during these analyses.

Low-level laser therapy versus wrist splint and non-steroidal anti-inflammatory drugs

One randomised trial involving 42 participants (21 randomised to LLLT) compared LLLT to wrist splint and NSAIDs (Rodrigues 2013).

Study characteristics

Participants

The trial included people with CTS as diagnosed by the study authors via clinical findings and NCS. The mean age in the trial was 50 to 59 years and 95% of the participants were female.

Interventions

The types of LLLT and wrist splint with NSAIDs used in the trial are described in the Characteristics of included studies table.

Risk of bias in included studies

The trial was at high risk of bias. This is summarised in the 'Risk of bias' summary figure (Figure 2).

We did not produce a 'Summary of findings' table for this comparisons as no data for any prespecified outcomes were available. The reported outcomes were assessed at short term (less than three months) follow-up. The authors did not investigate long-term outcomes.

Secondary outcomes

Nerve conduction studies

The study authors categorised the NCS findings into mild, moderate, and severe. We converted them to continuous outcomes (1, 2, and 3, respectively). Analysis of the study authors' findings revealed no significant difference in the improvement in NCS of people treated with LLLT compared to wrist splint and NSAIDs (MD -0.48, 95% CI -0.98 to 0.02; P = 0.06). The GRADE quality of evidence was very low.

Any other measure of improvement in symptoms or function: symptom improvement questionnaires

The study authors categorised symptoms as: without pain, light pain, moderate pain, and severe pain. In the LLLT group, the percentage in each of these categories were, respectively, 9.6%, 19%, 52.4%, and 19% before treatment versus 66.6%, 23.8%, 9.6%, and 0% after treatment. Corresponding data for the wrist splint and NSAID group were 0%, 4.8%, 61.8% and 33.4% before treatment versus 4.8%, 57.2%, 38%, and 0% after treatment.

Unreported outcomes

The study authors did not measure or report on the following outcomes: overall improvement in carpal tunnel syndrome: SSS, overall improvement in carpal tunnel syndrome: FSS, VAS pain, strength measured by dynamometry (grip strength and finger-pinch strength), and adverse events.

Low-level laser therapy versus tendon gliding exercises

One randomised trial involving 30 participants (15 randomised to LLLT) compared LLLT to TGEs (Atya 2011).

Study characteristics

Participants

The trial included people with CTS as diagnosed by the trial authors via clinical findings and NCS. All participants were female, and the mean age was 38 years.

Interventions

The types of LLLT and TGE used in the trial are described in the Characteristics of included studies table.

Risk of bias in included studies

The trial was at high risk of bias. This is summarised in the 'Risk of bias' summary figure (Figure 2).

Secondary outcomes

Visual analogue score pain

An increase in VAS pain represents worsened pain. The scale ranged from 0 to 10, with an MCID of 1.2.
The study authors reported a decrease in VAS pain of people treated with LLLT compared to TGE (MD -2.34, 95% CI -3.35 to -1.33; P < 0.001).

Strength measured by dynamometry: grip strength

The study authors reported an increase in the grip strength of people treated with LLLT compared to TGE (MD 4.6 kg, 95% CI 2.73 to 6.47; P < 0.001). The GRADE quality of evidence was very low.

Nerve conduction studies

The study authors reported a significant difference in NCS of people treated with LLLT compared to TGE, favouring LLLT for motor latency (MD -0.82 ms, 95% CI -1.18 to -0.46; P < 0.001), sensory latency (MD -0.33 ms, 95% CI -0.54 to -0.12; P = 0.002), and sensory conduction velocity (MD 1.74 m/s, 95% CI 0.60 to 2.88; P = 0.003). The GRADE quality of evidence of these outcomes was very low.

Unreported outcomes

The study authors did not measure or report on the following outcomes: overall improvement in carpal tunnel syndrome: SSS, overall improvement in carpal tunnel syndrome: FSS, strength measured by dynamometry (finger-pinch strength), adverse events, and any other measure of improvement in symptoms or function.

Low-level laser therapy (as part of multiple interventions) versus other non-surgical interventions

Low-level laser therapy and wrist splint versus ultrasound and wrist splint

One randomised trial involving 60 participants with 120 symptomatic wrists (100 wrists completed, 36 wrists randomised to LLLT, number of participants randomised to LLLT not stated) compared LLLT and splint to ultrasound and wrist splint (Dincer 2009).

Study characteristics

Participants

The trial included people with CTS as diagnosed by the study authors via NCS. The mean age of participants was 46 years and 100% were female. This trial analysed its unit of analysis as wrists (including bilateral), not participants, and underwent subsequent sensitivity analysis.

Interventions

The types of LLLT, wrist splint, and ultrasound used in the trial are described in the Characteristics of included studies table.

Risk of bias in included studies

The trial was at high risk of bias. The risk of bias is summarised in the 'Risk of bias' summary figure (Figure 2).

Primary outcomes

Overall improvement: Symptom Severity Score

An increase in SSS represents increased severity of symptoms. The scale ranged from 1 to 5, with an MCID of 1.14.
The study authors reported a significant decrease in SSS of LLLT and wrist splint versus ultrasound and wrist splint (MD -0.71, 95% CI -1.06 to -0.36; P = 0.0003). The GRADE quality of evidence was very low. The findings did not meet the MCID. See Summary of findings 4 for details.

Overall improvement: Functional Status Scale

An increase in FSS represents worsened disability. The scale ranged from 1 to 5, with an MCID of 0.74.
The study authors reported no significant differences in FSS of LLLT and wrist splint versus ultrasound and wrist splint (MD

-0.18, 95% CI -0.46 to 0.10; P = 0.18). The GRADE quality of evidence was very low. The findings did not meet the MCID.

Secondary outcomes

Visual analogue score pain

An increase in VAS pain represents worsened pain. The scale ranged from 0 to 10, with an MCID of 1.2.
The study authors reported a significant decrease in VAS pain of LLLT and wrist splint versus ultrasound and wrist splint (MD -1.25, 95% CI -2.28 to -0.22; P = 0.008). The GRADE quality of evidence was very low. The findings did not meet the MCID.

Nerve conduction studies

The study authors reported numerical values for sensory velocity and motor distal latency only. They reported no significant difference between LLLT and wrist splint versus ultrasound and wrist splint in sensory velocity (MD 2.67 m/s, 95% CI -1.04 to 6.38; P = 0.11) or motor latency (MD -0.07 ms, 95% CI -0.21 to 0.07; P = 0.36). The GRADE quality of evidence for both outcomes was very low.

Unreported outcomes

The study authors did not measure or report on the following outcomes: strength measured by dynamometry (grip strength and finger-pinch strength), adverse events and any other measure of improvement in symptoms or function.

Sensitivity analysis

The unit of analysis used was wrists, not participants. We performed a sensitivity analysis to account for a clustering unit-of-analysis error. The interpretation of the effect estimate did not change for any outcome during this analysis.

Low-level laser therapy and wrist splint versus placebo LLLT and wrist splint

One randomised trial involving 66 participants with 112 symptomatic wrists (112 wrists completed, 56 wrists randomised to LLLT, number of participants randomised to LLLT not stated) compared LLLT and wrist splint to placebo LLLT and wrist splint (Fusakul 2014).

Study characteristics

Participants

The trial included people with CTS as diagnosed by the study authors via NCS. The mean age of participants was 51 years and 96% were female. This trial analysed its unit of analysis as wrists (including bilateral), not participants, and underwent subsequent sensitivity analysis.

Interventions

The types of LLLT and splint used in the trial are described in the Characteristics of included studies table.

Risk of bias in included studies

The trial was at high risk of bias. The risk of bias is summarised in the 'Risk of bias' summary figure (Figure 2).

Primary outcomes

Overall improvement: Symptom Severity Score

An increase in SSS represents increased severity of symptoms. The scale ranged from 1 to 5, with an MCID of 1.14.
The study authors reported no significant differences in SSS of LLLT and wrist splint versus placebo LLLT and wrist splint (MD 0.14, 95% CI -0.06 to 0.34; P = 0.17). The GRADE quality of evidence was very low. The findings did not meet the MCID. See Summary of findings 5 for details.

Overall improvement: Functional Status Scale

An increase in FSS represents worsened disability. The scale ranged from 1 to 5, with an MCID of 0.74.
The study authors reported no significant differences in FSS of LLLT and wrist splint versus placebo LLLT and wrist splint (MD 0.16, 95% CI -0.04 to 0.36; P = 0.11). The GRADE quality of evidence was very low. The findings did not meet the MCID.

Secondary outcomes

Visual analogue score pain

An increase in VAS pain represents worsened pain. The scale ranged from 0 to 10, with an MCID of 1.2.
The study authors reported a significant increase in VAS pain of LLLT and wrist splint versus placebo LLLT and wrist splint (MD 0.97, 95% CI 0.83 to 1.11; P < 0.00001). The GRADE quality of evidence was very low. The findings did not meet the MCID.

Strength measured by dynamometry: grip strength

The study authors reported a significant increase in grip strength of LLLT and wrist splint versus placebo LLLT and wrist splint (MD 0.89 kg, 95% CI 0.49 to 1.29; P < 0.00001). The GRADE quality of evidence was very low. The findings did not meet the MCID.

Strength measured by dynamometry: finger-pinch strength

The study authors reported no significant differences in finger-pinch strength of LLLT and wrist splint versus placebo LLLT and wrist splint (MD -0.07 kg, 95% CI -0.18 to 0.04; P = 0.21). The GRADE quality of evidence was very low. The findings did not meet the MCID.

Nerve conduction studies

The study authors reported a significant decrease in sensory latency (MD -0.18 ms, 95% CI -0.24 to -0.12; P < 0.00001) and motor latency (MD -1.90 ms, 95% CI -2.19 to -1.61; P < 0.00001) with a significant increase in sensory amplitude (MD 1.09 μV, 95% CI 0.44 to 1.74; P = 0.001) and no significant changes for motor amplitude (MD 0.01 mV, 95% CI -0.12 to 0.14; P = 0.88) of LLLT and wrist splint versus placebo LLLT and wrist splint. The changes noted in NCS did not represent a clinically important difference (Padua 1997).

Adverse events

The study authors reported that two participants experienced pain of a mild degree in both hands: one received laser therapy and the other received placebo laser. A further two participants had experienced discomfort of tingling sensation during laser treatment only in the hand which received laser therapy but not in the other hand which received placebo laser. Based on this, we observed no significant difference in adverse events between LLLT and a wrist splint versus placebo LLLT and a wrist splint (RR 2.00, 95% CI 0.38 to 10.48; P = 0.41).

Unreported outcomes

The study authors did not measure or report on the following outcome: any other measure of improvement in symptoms or function.

Sensitivity analysis

The unit of analysis used was wrists, not participants. We performed a sensitivity analysis to account for a clustering unit-of-analysis error. The interpretation of the effect estimate did not change for any outcome during this analysis.

Low-level laser therapy, a wrist splint, and vitamin B_6 versus placebo low-level laser therapy, a wrist splint, and vitamin B_6

One randomised trial involving 50 participants (18 randomised to LLLT) compared LLLT, a wrist splint, and vitamin B_6 to placebo LLLT, a wrist splint, and vitamin B_6 (Rayegani 2013).

Study characteristics

Participants

The trial included people with CTS as diagnosed by the study authors via clinical findings and NCS. The mean age of participants was 49 years. Information on gender was not available.

Interventions

The types of LLLT and splint used in the trial are described in the Characteristics of included studies table.

Risk of bias in included studies

The trial was at high risk of bias. The risk of bias is summarised in the 'Risk of bias' summary figure (Figure 2).

Primary outcomes

Overall improvement: Symptom Severity Score

The study authors reported using, and referenced, SSS but they provided results outside the normal range (1 to 5). As such, the range or MCID was unknown. Further information regarding this was not available in the text. From our analysis, we observed a significant increase in SSS of the LLLT group versus placebo group (MD 3.50, 95% CI 0.29 to 6.71; P = 0.03). The GRADE quality of evidence was very low. However, the study authors stated that there were no significant differences in improved disability between groups. Further information was not provided. We contacted trial authors for further information; however, this was not provided. See Summary of findings 6 for details.

Overall improvement: Functional Status Scale

The study authors reported to using, and referencing, FSS but they provided results outside the normal range (1 to 5). As such, the range or MCID was unknown. The study authors reported no significant differences in FSS of the LLLT group versus placebo LLLT group (MD -0.70, 95% CI -2.76 to 1.36; P = 0.45). The GRADE quality of evidence was very low. See Summary of findings 6 for details.

Secondary outcomes

Visual analogue score pain

An increase in VAS pain represents worsened pain. The scale ranged from 0 to 10, with an MCID of 1.2.

The study authors reported no significant difference in VAS pain of the LLLT group versus placebo LLLT group (MD 0.90, 95% CI -1.03 to 2.83; P = 0.08). The GRADE quality of evidence was very low.

Nerve conduction studies

The study authors reported no significant difference in sensory latency (MD 0.20 ms, 95% CI -0.33 to 0.73; P = 0.46), motor latency (MD 0.30 ms, 95% CI -0.16 to 0.76; P = 0.20), sensory amplitude (MD -2.00 μV, 95% CI -13.05 to 9.05; P = 0.72), or motor amplitude (MD -0.40 mV, 95% CI -2.46 to 1.66; P = 0.70) of the LLLT group versus placebo LLLT group. The GRADE quality of evidence for all outcomes was very low.

Unreported outcomes

The study authors did not measure or report on the following outcomes: strength measured by dynamometry (grip strength and finger-pinch strength), adverse events, and any other measure of improvement in symptoms or function.

ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

Low-level laser therapy compared to ultrasound for carpal tunnel syndrome

Patient or population: carpal tunnel syndrome
Setting:
Intervention: low-level laser therapy
Comparison: ultrasound

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with ultrasound	Risk with low-level laser therapy				
Overall improvement in CTS: SSS: short term (< 3 months) Scale from: 1 to 5	The mean overall improvement (as measured by SSS) short term (< 3 months) was 1.8	MD 0.43 higher (0.36 higher to 0.5 higher)	-	127 (2 RCTs)	⊕◯◯◯ Very low [1,2,3,4]	-
Overall improvement in CTS: SSS: long term Scale from: 1 to 5 Follow-up: mean 12 months	The mean overall improvement (as measured by SSS) long term was 2	MD 0.2 higher (0.55 lower to 0.95 higher)	-	27 (1 RCT)	⊕◯◯◯ Very low [1,3,4,5]	-
Overall improvement in CTS: FSS: short term (< 3 months) Scale from: 1 to 5	The mean FSS short term (< 3 months) was 1.9	MD 0.35 higher (0.29 higher to 0.41 higher)	-	127 (2 RCTs)	⊕◯◯◯ Very low [1,2,3,4]	-
Overall improvement in CTS: FSS: long term Scale from: 1 to 5 Follow-up: mean 12 months	The mean FSS long term was 2.2	MD 0 (0.075 lower to 0.75 higher)	-	27 (1 RCT)	⊕◯◯◯ Very low [1,3,4,5]	-

Adverse events	-	-	-	-	-	No adverse events reported in any trial.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **CTS:** carpel tunnel syndrome; **FSS:** Functional Status Scale; **MD:** mean difference; **RCT:** randomised controlled trial; **SSS:** Symptom Severity Score.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] High risk of bias.
[2] Little overlap of confidence intervals and heterogeneity in magnitude of effect.
[3] Total sample size under 400 in total in both groups.
[4] Because of the few trials, we were unable to assess publication bias by funnel plot.
[5] Only one trial.

Low-level laser therapy compared to fascial manipulation for carpal tunnel syndrome

Patient or population: carpal tunnel syndrome
Setting:
Intervention: low-level laser therapy
Comparison: fascial manipulation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with fascial manipulation	Risk with low-level laser therapy				
Overall improvement in CTS: SSS: short term (< 3 months) Scale from: 1 to 5	The mean overall improvement (as measured by SSS) short term (< 3 months) was 1.28	MD 1.72 higher (1.6 higher to 1.84 higher)	-	70 (1 RCT)	⊕◯◯◯ Very low [1,2,3,4]	-
Overall improvement in CTS:SSS: long term - not reported	-	-	-	-	-	-
Overall improvement in CTS: FSS: short term (< 3 months) Scale from: 1 to 5	The mean FSS short term (< 3 months) was 1.32	MD 1.31 higher (1.02 higher to 1.6 higher)	-	70 (1 RCT)	⊕◯◯◯ Very low [1,2,3,4]	-
Overall improvement in CTS: FSS: long term	-	-	-	-	-	Not reported.
Adverse events	-	-	-	-	-	Not reported.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **CTS:** carpel tunnel syndrome; **FSS:** Functional Status Scale; **MD:** mean difference; **RCT:** randomised controlled trial; **SSS:** Symptom Severity Score.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] High risk of bias.
[2] Total sample size under 400 in both groups.
[3] Only one trial.
[4] Because of the few trials, we were unable to assess publication bias by funnel plot.

Low-level laser therapy and a splint compared to ultrasound and a splint for carpal tunnel syndrome

Patient or population: carpal tunnel syndrome
Setting:
Intervention: low-level laser therapy + splint
Comparison: ultrasound + splint

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with ultrasound and a splint	Risk with low-level laser therapy and a splint				
Overall improvement in CTS:SSS: short term (< 3 months) Scale from: 1 to 5	The mean overall improvement (as measured by SSS) short term (< 3 months) was -0.95	MD 0.71 lower (1.06 lower to 0.36 lower)	-	66 (1 RCT)	⊕◯◯◯ Very low [1,2,3,4]	-
Overall improvement in CTS:SSS: long term - not measured	-	-	-	-	-	-
Overall improvement in CTS: FSS: short term (< 3 months) Scale from: 1 to 5	The mean FSS short term (< 3 months) was -0.80	MD 0.18 lower (0.46 lower to 0.10 higher)	-	66 (1 RCT)	⊕◯◯◯ Very low [1,2,3,4]	-
Overall improvement in CTS: FSS: long term - not reported	-	-	-	-	-	-
Adverse events	-	-	-	-	-	Not reported.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **CTS:** carpel tunnel syndrome; **FSS:** Functional Status Scale; **MD:** mean difference; **RCT:** randomised controlled trial; **SSS:** Symptom Severity Score.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] High risk of bias.
[2] Total sample size under 400 in total in both groups.
[3] Only one trial.
[4] Because of the few trials, we were unable to assess publication bias by funnel plot.

Low-level laser therapy and a splint compared to placebo and a splint for carpal tunnel syndrome

Patient or population: carpal tunnel syndrome
Setting:
Intervention: low-level laser therapy and a splint
Comparison: placebo and a splint

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo and a splint	Risk with low-level laser therapy and a splint				
Overall improvement in CTS: SSS: short term (< 3 months) Scale from: 1 to 5	The mean overall improvement (as measured by SSS) short term (< 3 months) was 1.35	MD 0.14 higher (0.06 lower to 0.34 higher)	-	112 (1 RCT)	⊕◯◯◯ Very low [1,2,3,4]	-
Overall improvement in CTS: SSS: long term - not measured	-	-	-	-	-	-
Overall improvement in CTS: FSS: short term (< 3 months) Scale from: 1 to 5	The mean FSS short term (< 3 months) was 1.37	MD 0.16 higher (0.04 lower to 0.36 higher)	-	112 (1 RCT)	⊕◯◯◯ Very low [1,2,3,4]	-
Overall improvement in CTS: FSS: long term - not measured	-	-	-	-	-	-
Adverse events	Study population		RR 2.00 (0.38 to 10.48)	112 (1 RCT)	⊕◯◯◯ Very low [1,2,3,4]	-

	36 per 1000	71 per 1000 (14 to 374)	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **CTS:** carpel tunnel syndrome; **FSS:** Functional Status Scale; **MD:** mean difference; **RCT:** randomised controlled trial; **RR:** risk ratio; **SSS:** Symptom Severity Score.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] High risk of bias.
[2] Total sample size under 400 in total in both groups.
[3] Only one trial.
[4] Because of the few trials, we were unable to assess publication bias by funnel plot.

Low-level laser therapy, wrist splint, and vitamin B_6 compared to placebo, wrist splint, and vitamin B_6 for carpal tunnel syndrome

Patient or population: carpal tunnel syndrome
Setting:
Intervention: low-level laser therapy, wrist splint, and vitamin B_6
Comparison: placebo, wrist splint, and vitamin B_6

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo + wrist splint + vitamin B_6	Risk with low-level laser therapy + wrist splint + vitamin B_6				
Overall improvement in CTS: SSS: short term (< 3 months) Scale unknown	The mean overall improvement (as measured by SSS) short term (< 3 months) was 3	MD 3.50 higher (0.29 higher to 6.71 higher)	-	33 (1 RCT)	⊕◯◯◯ Very low [1,2,3,4]	-
Overall improvement in CTS: SSS: long term - not measured	-	-	-	-	-	-
Overall improvement in CTS: FSS: short term (< 3 months) Scale not known	The mean FSS short term (< 3 months) was 4.4	MD 0.7 lower (2.76 lower to 1.36 higher)	-	33 (1 RCT)	⊕◯◯◯ Very low [1,2,3,4]	-
Overall improvement in CTS: FSS: long term - not reported	-	-	-	-	-	-
Adverse events	-	-	-	-	-	Not reported.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **CTS:** carpel tunnel syndrome; **FSS:** Functional Status Scale; **MD:** mean difference; **RCT:** randomised controlled trial; **SSS:** Symptom Severity Score.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] High risk of bias.
[2] Total sample size under 400 in total in both groups.
[3] Only one trial.
[4] Because of the few trials, we were unable to assess publication bias by funnel plot.

DISCUSSION

Summary of main results

This systematic review and meta-analysis aimed to determine the effectiveness and associated risk of LLLT compared with placebo or other non-surgical treatments for improving clinical and electrophysiological outcomes in people with CTS. The review included 22 trials randomising 1153 participants; nine studies compared LLLT with placebo, two studies compared LLLT with ultrasound, one study compared LLLT with placebo and LLLT with ultrasound, two studies compared LLLT with steroid injection, and one each compared LLLT with other non-surgical interventions: fascial manipulation, PMF, TENS, TGEs, and wrist splint with NSAIDs. Three trials compared LLLT as part of multiple interventions: one compared LLLT and applying a wrist splint with ultrasound and applying a wrist splint; one compared LLLT and applying a wrist splint with placebo and applying a wrist splint; and one compared LLLT, applying a wrist splint, and vitamin B6 with placebo LLLT, applying a wrist splint, and vitamin B6.

Irvine 2004 was at low risk of bias. All other included studies were at high or unclear overall risk of bias. Many were not blinded. The quality of the studies across outcomes for each intervention was largely very low, and any point estimates of effect or harm should be interpreted with great caution. Even without this fact, the effect sizes seen were modest or small and may not have any clinical relevance. Overall, there is insufficient evidence to establish any effect of LLLT over placebo or other non-surgical interventions for CTS. Limited and very low quality evidence exists for the effects of LLLT in the treatment of CTS and we found no data to support any clinically useful effect of LLLT in treating CTS. There is very low-quality evidence that LLLT may result in a greater improvement in VAS pain, motor nerve latency, and sensory nerve latency, and low-quality evidence that LLLT may result in a greater improvement in grip and finger-pinch strength, when compared with placebo at short-term (under three months) follow-up but the magnitude of any effect, although statistically significant, is of little benefit clinically.

The changes noted in NCSs are minimal and do not represent clinically important differences (Padua 1997). We could not define the MCID for grip and finger-pinch strength for people with CTS from any literature. They have been reported in healthy people, however, as 2.69 kg for grip strength and 0.68 kg for finger-pinch strength (Villafañe 2014). Based on this, we interpreted our findings as a clinically insignificant change for grip strength (2.58 kg) and in meeting the MCID for pinch-strength (0.94 kg).

There is very low-quality evidence that LLLT may result in a lesser improvement in VAS pain and motor nerve latency and low-quality evidence that LLLT may result in a lesser improvement in finger-pinch strength and motor nerve amplitude when compared with ultrasound at short-term follow-up. These results are also as sensitive to bias as those indicating improvement in the opposite direction.

One trial examining long-term (12-month) follow-up found no significant improvements in VAS pain, SSS, FSS, grip strength, or NCS for LLLT compared to placebo or ultrasound.

For short-term outcomes from other non-surgical interventions, LLLT versus fascial manipulation favoured fascial manipulation for SSS, FSS, and VAS pain. LLLT versus PMF found no significant differences in VAS pain or NCS. LLLT versus TENS favoured LLLT for VAS pain and NCS (motor latency, sensory nerve conduction velocity). LLLT versus steroid injection revealed a significant difference in symptom improvement questionnaires favouring steroid injection, but there were significant differences for VAS pain or NCS. Lucantoni 1992 also examined long-term follow-up, for which there was no significant difference between LLLT and steroid injection. LLLT versus TGEs favoured LLLT for VAS pain, grip strength, and NCS (motor latency, sensory latency, and sensory conduction velocity). LLLT versus wrist splint and NSAIDs favoured LLLT for symptom improvement questionnaires but there was no significant difference with NCS. LLLT versus TENS was at unclear risk of bias; all other non-surgical intervention trials were at high risk of bias and their results should be interpreted with great caution. A series of small studies of this type will usually overestimate the beneficial effects.

Only one study, Fusakul 2014, reported adverse events. They reported adverse events in four wrists (8%) consisting of mild wrist pain in two and discomfort during treatment in two. After the end of laser treatment, these symptoms resolved.

Overall completeness and applicability of evidence

For assessment of risk of bias, several of the included studies did not report information on important factors regarding study conduct. These included details about the method of random sequence generation, allocation concealment, method of blinding, methods used to handle missing data, and handling of bilateral wrist data to avoid unit-of-analysis error, all of which result in bias. For example, the authors of 12 studies did not report sufficient information to determine if they used an adequate method of allocation concealment. This is an important aspect of study conduct which meta-analysis of epidemiological evidence suggests can result in biased treatment effects (Savović 2012).

The mean age ranged from 46 to 54 years in LLLT versus placebo trials and 36 to 48 years in LLLT versus ultrasound trials. The results of this meta-analysis apply to populations with a similar age demographic.

Only one study, Tascioglu 2012, compared different regimens of LLLT and no studies provided a comparative assessment of LLLT delivered over different time scales (e.g. three weeks of LLLT treatment compared to three months). Therefore, there is insufficient evidence regarding the optimum duration of LLLT treatment.

Only one study, Fusakul 2014, reported on adverse events. Other studies did not specify within the results if no adverse events oc-

curred and so conclusions regarding adverse events cannot be made as the evidence is lacking.

The included studies were limited in the duration of follow-up for outcome assessment. Only one study assessed the long-term effects of LLLT versus placebo or LLLT versus therapeutic ultrasound, and one assessed the long-term effects of LLLT versus steroid injection. These trials showed no significant difference between LLLT and the comparison intervention across all outcomes (Lucantoni 1992; Tikiz 2013). No other studies assessed the long-term outcomes of LLLT versus any other comparator. We cannot, therefore, draw conclusions regarding the long-term outcomes of LLLT versus the comparators listed within this review.

Quality of the evidence

Risk of bias varied across the studies, but was generally high in most domains. All studies were small, ranging from 15 to 100 participants and therefore an overestimation of any effect is likely. Lack of participant blinding may have influenced the self-reported outcomes of VAS pain, SSS, and FSS.

There was inconsistency throughout all comparisons. Within the LLLT versus placebo comparison, all outcomes presented significant inconsistency. There was substantial and considerable heterogeneity across several outcomes: VAS pain (I^2 = 92%), SSS (I^2 = 98%), and FSS (I^2 = 89%). These outcomes also had little overlap of CIs, and heterogeneity in magnitude of effect. Grip and finger-pinch strength had no inconsistency across trials, both with a calculated I^2 statistic of 0% and CIs consistently overlapping. Although motor nerve latency and sensory nerve latency had an I^2 statistic of 0%, they had little overlap of CIs and heterogeneity in the direction of effect; therefore, we downgraded the quality of evidence. Within the LLLT versus ultrasound comparison, we noted substantial heterogeneity for VAS pain (I^2 = 89%) and moderate heterogeneity for motor amplitude (I^2 = 39%), with little overlap of CIs and heterogeneity in magnitude of effect for both outcomes. SSS and FSS had no heterogeneity, with good overlap of CIs and I^2 = 0%. There was little overlap of CIs and heterogeneity in the direction of effect across the outcomes grip strength (I^2 = 42%), motor latency (I^2 = 83%), and sensory latency (I^2 = 65%). Assessment of inconsistency was not possible in other outcomes or comparisons.

In the comparison LLLT versus placebo, motor latency had no imprecision, with a sample size greater than 400 in total in both groups and the CIs not including the MCID on either side of zero. We downgraded the quality of evidence for imprecision for all other outcomes in LLLT versus placebo and downgraded the quality of evidence for imprecision across all other comparisons due to the total study sample size being less than 400.

We intended to draw funnel plots to distinguish between publication bias and other causes of asymmetry. However, there were insufficient studies to conduct these analyses. Caution should be taken in the interpretation of the results in light of possible publication bias.

Potential biases in the review process

We made all efforts to minimise bias in this systematic review and meta-analysis process. We conducted this systematic review and meta-analysis in accordance with the PRISMA reporting guidelines for the conduct of meta-analysis of interventional trials. We published a trial protocol prior to commencement of the systematic review (Other published versions of this review). We searched four electronic databases using search strategies suitable for identification of RCTs. There were no limitations to the search with regards to language or publication status. We handsearched reference lists of studies for further references and we searched clinical trial registries for ongoing studies. Two review authors independently carried out selection of studies, data extraction, and 'Risk of bias' with disagreements resolved through a third independent review author. This decreased the risk of bias within the review process. Further databases that could have been searched to identify additional trials include the Cochrane Neuromuscular Specialised Register and allied health databases such as Allied and Complementary Medicine Database (AMED), Cumulative Index to Nursing and Allied Health Literature (CINAHL), or Physiotherapy Evidence Database (PEDro).

Limitations include difficulty obtaining relevant unpublished data from authors of included studies. We could not find protocols or trial registry entries for the included studies, which restricted our ability to assess selective outcome reporting. Only one trial reported adverse events and all studies were small in participant numbers. With this regard, rare adverse events were unlikely to have been detected from trial data. The review was initially undertaken as a thesis with Cochrane Neuromuscular and subsequently adapted to comply with Cochrane publishing guidelines. Cochrane Neuromuscular states preference within published guidance for one primary outcome and up to five secondary outcome measures. As such, we changed primary and secondary outcomes from the original protocol to comply with this. SSS and FSS remained as the primary outcome measure (overall improvement) while we changed the remaining primary outcomes to secondary outcomes. Secondary outcomes were grouped where possible (while previously grip strength and finger-pinch strength were separate outcomes, they are now paired as dynamometry). All outcomes from the initial protocol were included within the text and reported separately however to reduce selective reporting bias. No other changes were made to the protocol. In the initial thesis, all outcomes were listed for inclusion within the 'Summary of findings' tables. The selection of outcomes for inclusion in the 'Summary of findings' tables in this review is therefore retrospective and a potential bias in the review process.

Agreements and disagreements with other studies or reviews

We found one limited systematic review and meta-analysis on the topic (Li 2016). The Li 2016 meta-analysis included seven studies: four LLLT versus placebo and three LLLT in conjunction with a splint versus placebo. Six of the studies were included within this review, one was excluded for comparing LLLT with a splint versus a splint with no placebo (Yagci 2009). Li 2016 meta-analysed LLLT versus placebo alongside LLLT in conjunction with another therapy versus placebo, therefore the results should be interpreted with caution. Li 2016 found that LLLT improved grip strength, VAS pain, and sensory nerve motor amplitude.

The findings in this review are in agreement with systematic reviews of LLLT for the pain management of other pathologies (non-specific low-back pain, neck pain, and orthodontic pain), which concluded that there were insufficient data to draw firm conclusions (Kadhim-Saleh 2013; Li 2015; Ren 2015; Yousefi-Nooraie 2008).

AUTHORS' CONCLUSIONS

Implications for practice

Limited and very low-quality evidence exists on the effects of low-level laser therapy (LLLT) in the treatment of carpal tunnel syndrome (CTS). The included trials were of very low quality and found no data to support any clinical effect of LLLT in treating CTS. Only visual analogue scale (VAS) pain and finger-pinch strength meet previously published minimal clinically important differences (Kelly 2001; Villafañe 2014), but these are likely to be overestimates of effect given the small studies and significant risk of bias. There is low- or very low-quality evidence to suggest that LLLT may be less effective than ultrasound in the management of CTS for short-term, clinically significant improvements in pain and finger-pinch strength. With regards to ultrasound, one Cochrane systematic review has previously concluded that there is only poor-quality evidence from very limited data to suggest that ultrasound may be more effective than placebo for either short- or long-term symptom improvement in people with CTS (Page 2013). Both reviews highlight the low quality of evidence for these interventions.

There is insufficient evidence to indicate whether LLLT is more or less effective than placebo or ultrasound in the management of CTS at long-term follow-up, based on improvement in clinical findings and nerve conduction studies. The available evidence is of very low quality and as such it is uncertain whether LLLT improves or worsens any of the primary or secondary outcomes reported. There is insufficient evidence to support or refute greater benefit with LLLT than other types of non-surgical treatment in the management of CTS.

Implications for research

Any further research of LLLT should be definitive, blinded, and of high quality. The existing very low-quality evidence does not need replicating. Trials should assess the long-term effects of treatment. Trials should report adverse events as an outcome. Future randomised controlled trials of LLLT versus placebo are first needed to ascertain any significant therapeutic effect of LLLT. Trials should ensure an adequate method of random sequence generation and allocation concealment. Blinding methods of participants, personnel, and outcome assessors need to be fully described and blinding success assessed (such as by asking participants to indicate which intervention they believe they received). Patient-oriented and healthcare planning-oriented outcomes should be included. Appropriate methods such as multiple imputation, 'best-worst' case scenario and 'worst-best' case scenario sensitivity analysis to handle missing data need to be performed. More trials assessing LLLT versus other non-surgical treatments need to adopt blinding of participants and personnel. Any future trials should be conducted and reported according to the CONSORT statement (Schulz 2011).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aigner 1999

Methods	Randomised controlled trial
Participants	Country: Germany Number randomised: 26 Postrandomisation dropouts: 0 Mean age: 54 years Females: 20 (77%) Inclusion criteria: • Clinical evidence of CTS Exclusion criteria: • Diabetes mellitus • Chronic alcoholism • Previous operation for CTS
Interventions	Group 1: LLLT (n = 13) Group 2: placebo (n = 13) Intervention (group 1): 5 mW helium-neon laser, 15 s at each point (632.6 nm wavelength) at 6 acupuncture points around the wrist for 15 s at each point Comparator (group 2): placebo laser
Outcomes	Paraesthesia in digits, night pain, activity associated pain, Tinel's sign, nerve conduction velocity, distal latency, total potential (did not specify motor or sensory)
Notes	Short-term follow-up (< 3 months)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "single-blind study." Comment: placebo laser used, participants likely blinded but healthcare providers not
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "single-blind study" Comment: further details not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts

Aigner 1999 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Comment: some important outcomes that would generally be assessed were not reported. No protocol or trial registry entry identified
Other bias	Unclear risk	Unclear if free of vested interest bias, information not available

Atya 2011

Methods	Randomised controlled trial
Participants	Country: Egypt Number randomised: 30 Postrandomisation dropouts: 0 Mean age: 38 years Females: 30 (100%) Inclusion criteria: • Clinical and electrophysiological evidence of CTS Exclusion criteria: • Secondary entrapment neuropathies • Axonal degeneration • Previous LLLT • Steroid injection or regular analgesic for CTS • Thyroid disease • Diabetes • Pregnancy • Systemic peripheral neuropathy
Interventions	Group 1: LLLT (n = 15) Group 2: tendon and nerve gliding exercises (n = 15) Intervention: gallium-aluminium-arsenide laser (Enraf, Endolaser) wavelength 830 nm, output power 30 mW. Total dose per treatment 9 J, accumulated dose 72 J Comparator: tendon gliding exercises
Outcomes	VAS (pain), grip strength, NCS (motor latency, sensory latency, sensory nerve conduction velocity)
Notes	Short-term follow-up (< 3 months)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available

Atya 2011 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: blinding of participants not possible due to different intervention types
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: all important outcomes were reported. No protocol or trial registry entry identified
Other bias	Unclear risk	Comment: information not available

Bakhtiary 2004

Methods	Randomised controlled trial
Participants	Country: Iran Number randomised: 50 Postrandomisation dropouts: 0 Mean age: 46 years Females: information not available Inclusion criteria: • Clinical and electrophysiological evidence of CTS Exclusion criteria: • Secondary entrapment neuropathy • Axonal degeneration • Previously treated with ultrasound, LLLT, steroid injection • NSAID/analgesic treatment • Thyroid disease • Diabetes • Systemic peripheral neuropathy
Interventions	Group 1: LLLT (n = 25) Group 2: ultrasound (n = 25) Intervention LLLT: 9 J infrared laser diode, 830 nm at 5 points (1.8 J/point) Comparator ultrasound: frequency of 1 MHz and intensity of 1.0 W/cm^2, Enraf Sonopuls 434 machine
Outcomes	VAS, grip strength, finger-pinch strength, NCS (sensory latency and amplitude, motor latency, and amplitude)
Notes	Short-term follow-up (< 3 months)
Risk of bias	

Bakhtiary 2004 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer generated randomisation list"
Allocation concealment (selection bias)	Low risk	Quote: "sealed numbered envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The staff who assessed the outcomes were different from the staff administering the treatments and they were blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: all important outcomes were reported. No protocol or trial registry entry identified
Other bias	Low risk	Quote: "grant from Semnan Medical Sciences University" Vested interest bias low risk

Casale 2013

Methods	Randomised clinical trial
Participants	Country: Italy Number randomised: 20 Postrandomisation dropouts: 0 Mean age: 38 years Females: 10 (50%) Inclusion criteria: • Clinical and electrophysiological evidence of CTS Exclusion criteria: • Abnormal findings in ulnar NCS, such as in cases of polyneuropathies of various aetiology (diabetic, uraemic) and more proximal neuropathies
Interventions	Group 1: LLLT (n = 10) Group 2: transcutaneous electrical nerve stimulation (n = 10) 1 group was treated with sessions of 30 minutes of transcutaneous electrical stimulation set to administer rectangular waves of 80 ms width, 100 Hz frequency with intensity below muscle contraction, on pregel electrodes 35 × 45 mm place on the carpal ligament and proximally along the course of the median nerve. The other group was treated with combined 830-1064 nm Laser consisting of a radiation dose of 250 J/cm delivered to the skin overlying the course of the median nerve at the wrist for 100 s at 25 W

Casale 2013 (*Continued*)

Outcomes	VAS (pain), NCS (motor latency and sensory nerve conduction velocity)	
Notes	Short-term follow-up (< 3 months)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were assigned to one or other of the two treatment groups by means of a computer-aided allocation system"
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: stated participants blinded but did not state method of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Staff administered treatment and outcome measures were blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: all important outcomes were reported. No protocol or trial registry entry identified
Other bias	Unclear risk	Comment: information not available

Chang 2008

Methods	Randomised controlled trial
Participants	Country: Taiwan Number randomised: 40 Postrandomisation dropouts: 0 Mean age: 47 years Females: information not provided Inclusion criteria: • Clinical evidence of CTS • No surgery to the wrist • First onset of CTS > 1 year ago with repeated episodes • Never previously had laser therapy Exclusion criteria: • Rheumatoid arthritis • History of metabolic disease • Paralysed limbs caused by stroke

Interventions	Group 1: LLLT (n = 20) Group 2: placebo (n = 20) Intervention: "Painless light PL-830; Advanced Chips & Products Corp., Hillside, NJ," emitted 2 light beams spaced 2.5 cm apart via 2 laser diodes. The operational wavelength was 830 nm. Its output frequency and output power were set to be 10 Hz and 60 (2 × 30) mW, respectively Treatment dose was 9.7 J/cm^2. The laser was placed directly above the transverse carpal ligament (between the pisiform and navicular bones) on the person's affected wrist. The treatments were conducted by the same physical therapist over 2 weeks for 10 min per day, 5 days per week Comparator: placebo laser
Outcomes	SSS, FSS, grip strength, finger-pinch strength, NCS (sensory and motor latency)
Notes	Short-term follow-up (< 3 months)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: method of randomisation not given
Allocation concealment (selection bias)	Unclear risk	Comment: method of allocation concealment not given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: authors stated that a "double-blind experiment" was performed but no information provided on methods of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: authors stated that a "double-blind experiment" was performed but no information provided on methods of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: all important outcomes were reported. No protocol or trial registry entry identified
Other bias	Low risk	Quote: "The authors are grateful to the National Science Council of the Republic of China for financially supporting this research" No vested interest bias

Dakowicz 2011

Methods	Randomised controlled trial
Participants	Country: Poland Number randomised: 38 Postrandomisation dropouts: 0 Mean age: 51 years Females: 35 (92%) Inclusion criteria: • Clinical and electrophysiological evidence of CTS Exclusion criteria: None provided
Interventions	Group 1: LLLT (n = 18). Group 2: pulsed magnetic frequency (n = 20) Intervention: gallium-arsenide laser, "Physioter; D-50, ZEM MARP Electronic Krakow, Poland," wavelength 904 nm, power density 150 mW. The total energy per treatment 50 J Comparator: pulsed magnetic frequency, Magnetronic MF-10 "Elektronika Elektromedycyna Otwock, Poland" frequency 10-40 Hz, induction 1.0-5.0 mTesla
Outcomes	Day and night paraesthesia, day and night pain, VAS, Phalen's test, Tinel's test, armband test, NCS (sensory and motor latency)
Notes	Short-term follow-up (< 3 months)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not provided
Allocation concealment (selection bias)	Unclear risk	Comment: information not provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: participants not blinded to intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: all important outcomes were reported. No protocol or trial registry entry identified
Other bias	Unclear risk	Comment: information not provided

Dincer 2009

Methods	Randomised controlled trial
Participants	Country: Turkey Number randomised: 60 (120 wrists) Postrandomisation dropouts: n = information not available, 20 wrists Mean age: 46 years Females: 60 (100%) Inclusion criteria: • Diagnosed with mild to moderate CTS according to the American Association of Electrodiagnostic Medicine guidelines Exclusion criteria: • Severe CTS • Underlying metabolic disorders such as diabetes mellitus, thyroid or kidney disease • Connective tissue disorders • Malignancy • Distal radial fracture • Cervical radiculopathy • Brachial plexopathy • Tenosynovitis • Fibromyalgia • Any other CTS treatment or surgical procedure during the past year • Pregnant
Interventions	Group 1: wrist splint (n = 34 wrists) Group 2: wrist splint + ultrasound (n = 30 wrists) Group 3: wrist splint + LLLT (n = 36 wrists) Splint: neutral standard light-weight wrist splint worn at night and during aggravating daytime activities Ultrasound: administered to each hand for 3 min per session, with 10 sessions performed once per day, 5 times per week for 2 weeks. Ultrasound administered at frequency of 3 MHz and intensity of 1.0 W/cm^2 in continuous mode LLLT: infrared gallium-arsenide diode laser with wavelength 904 nm, frequency range 5-7000 Hz, pulse duration 200 ns, maximum power output 27 W, mean power 2.4 mW. LLLT applied to 3 points over course of median nerve for 30 s at each point, with 10 sessions performed once per day, 5 times per week for 2 weeks
Outcomes	VAS, SSS, FSS, patient satisfaction 5-point scale, NCS (motor latency, velocity and amplitude, sensory velocity and amplitude)
Notes	Short-term follow-up (< 3 months)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was performed by the use of numbered envelopes." Comment: unclear how, and whether or not, the ran-

Dincer 2009 (*Continued*)

		domisation sequence adequately generated
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization was performed by the use of numbered envelopes." Comment: unclear whether allocation sequence adequately concealed (i.e. whether numbered envelopes were sealed and opaque and sequentially numbered)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Ultrasound therapy was administered to each hand for 3 min per session, on the area over the carpal tunnel…with aquasonic gel;" "Laser therapy was applied to three points over the course of the median nerve at the wrist. The laser probe was applied directly and perpendicularly in contact with the skin for 30 sec at each point. At each treatment session, the patients and physiotherapist wore protective glasses. " Comment: different treatment methods and application make it likely blinding was not possible
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "at the first and third month the assessments were performed by another physiatrist who was blinded to treatment modality"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: postrandomisation dropouts with no methods to handle missing data
Selective reporting (reporting bias)	High risk	Comment: authors reported numerical outcomes for some but not all NCS data (motor latency and sensory velocity reported, for the remainder numerical data not given). No protocol or trial registry entry identified
Other bias	Low risk	Quote: "No conflicting financial interest exist."

Ekim 2007

Methods	Randomised controlled trial
Participants	Country: Turkey. Number randomised: 19 Postrandomisation dropouts: 0 Mean age: 52 years Females: 18 (95%) Inclusion criteria: • Clinical and electrophysiological evidence of CTS • Rheumatoid arthritis Exclusion criteria: • Underlying metabolic disorders

Ekim 2007 (*Continued*)

	• Cervical radiculopathy • Previous wrist trauma • Peripheral neuropathies • Anaesthesia or intractable pain due to CTS • Steroid injection or physiotherapy in last 3 months • Thenar atrophy • Spontaneous activity on NCS of the abductor pollicis brevis muscle
Interventions	Group 1: LLLT (n = 10) Group 2: placebo (n = 9) Intervention: gallium-aluminium-arsenid laser device (Endolaser 476 Enraf Nonius, Netherlands); power output 50 mW. Treatment dose 7.5 J and accumulated dose 75 J Comparator: placebo laser
Outcomes	VAS (pain), SSS, FSS, grip strength, NCS (motor latency and amplitude, sensory latency, and amplitude), Tinel's sign, Phalen's sign
Notes	Short-term follow-up (< 3 months)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: method of randomisation not available
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment information not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "another physician not blinded to treatment allocation applied the treatments"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "a blinded physician unaware of the treatment allocation performed the clinical and electrophysiological parameters at baseline, post treatment and a month 3"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: all important outcomes were reported. No protocol or trial registry entry identified
Other bias	Low risk	Quote: "No financial support declared"

Evcik 2007

Methods	Randomised controlled trial
Participants	Country: Turkey Number randomised: 81 Postrandomisation dropouts: 0 Mean age: 46 years Females: 70 (86%) Inclusion criteria: • Clinical and electrophysiological evidence of CTS Exclusion criteria: • Severe hand trauma • Cervical radiculopathy • Thoracic outlet syndrome • Neurological, cognitive, inflammatory, or tumoural disorders
Interventions	Group 1: LLLT (n = 41) Group 2: placebo (n = 40) Intervention: 830 nm aluminium-gallium-arsenide diode laser, maximum power output 450 mW. Laser therapy 7 J per point to 2 points in pulse mode with power density 0. 60 W/cm^2 by a pulse frequency 1000 Hz, 30 s irradiation at each point. Total of 10 treatments - once daily, 5 days per week for 2 weeks Comparator: placebo laser
Outcomes	VAS (pain), VAS (pain) night, SSS, grip strength, finger-pinch strength, NCS (motor latency, velocity and amplitude, sensory latency, velocity, and amplitude)
Notes	Short-term follow-up (< 3 months)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: allocation given in numbered envelopes, further information required for randomisation of envelopes
Allocation concealment (selection bias)	Low risk	Comment: allocation given in numbered envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "patients and physicians were not aware of the therapy"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "physicians were not aware of the therapy...post-treatment outcome measures were assessed by another physician"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts

Evcik 2007 (*Continued*)

Selective reporting (reporting bias)	High risk	Comment: SSS reported within text but FSS not reported. No protocol or trial registry entry identified
Other bias	Unclear risk	Vested interest bias unclear: information not available

Fusakul 2014

Methods	Randomised controlled trial
Participants	Country: Thailand Number randomised: 66 (112 wrists) Postrandomisation dropouts: 7 (112 wrists) Mean age: 51 years Females: 108/112 wrists (96%) Inclusion criteria: • mild to moderate CTS on NCS (as defined by American Association of Electrodiagnostic Medicine guidelines) Exclusion criteria: • Severe CTS • Underlying metabolic disorders • Previous distal radius fractures • Wrist-hand deformities • Inflammation of joints in hand such as rheumatoid arthritis
Interventions	Group 1: LLLT + splint (n = information not available, 56 hands) Group 2: placebo LLLT + splint (n = information not available, 56 hands) Intervention: gallium-aluminium-arsenide diode laser with wavelength 810 nm and power output 50 mW. Dose of treatment 18 J per session. Each participant treated with laser therapy for 15 sessions in total over 5 weeks Each participant also prescribed a prefabricated neoprene splint set in neutral position. All participants were encouraged to use their wrist splints during the night-time and daytime whenever possible Comparator: placebo laser
Outcomes	VAS, SSS, FSS, grip strength, finger-pinch strength, NCS (sensory latency and amplitude, motor latency, and amplitude)
Notes	Short-term follow-up (< 3 months)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomly allocated into two groups...by using two sets of previously prepared and randomly enumerated sealed envelopes that specified the treatment methods"

Fusakul 2014 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Comment: unclear whether allocation sequence was adequately concealed (i.e. whether numbered envelopes were sealed and opaque and sequentially numbered)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: authors stated that "double-blind experiment" was performed but no information provided on methods of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: authors stated that "double-blind experiment" was performed but no information provided on methods of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: postrandomisation dropouts with no methods to handle missing data
Selective reporting (reporting bias)	Low risk	Comment: all important outcomes were reported. No protocol or trial registry entry identified
Other bias	Low risk	Quote: "Each author certifies that he or she has no commercial associations that might pose a conflict of interest in connection with the submitted article...there was no external funding source outside of the University's Research Funding Program."

Irvine 2004

Methods	Randomised controlled trial
Participants	Country: Canada Number randomised: 15 Postrandomisation dropouts: 0 Mean age: 46 years Females: 12 (80%) Inclusion criteria: • Clinical and electrophysiological evidence of CTS Exclusion criteria: • Marked axonal loss on NCS • Arthritic disease • Previous wrist trauma • Previous carpal tunnel release
Interventions	Group 1: LLLT (n = 7) Group 2: placebo (n = 8) Intervention: gallium-aluminium-arsenide laser with wavelength 860 nm, dosage 6 J/cm^2 over carpal tunnel Comparator: placebo laser

Irvine 2004 (*Continued*)

Outcomes	SSS, FSS, Purdue pegboard test, NCS	
Notes	Short-term follow-up (< 3 months)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomization was done using the random-number generation function"
Allocation concealment (selection bias)	Low risk	Quote: "A staff person not involved in the rest of the study performed the randomization," "Neither the investigators nor the subjects were aware of the treatment assignment"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The physical therapist administering the treatments was not involved in the outcome measure assessment." "Neither the investigators nor the subjects were aware of the treatment assignment"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Neither the investigators nor the subjects were aware of the treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: all important outcomes were reported. No protocol or trial registry entry identified
Other bias	Low risk	Vested interest bias low. Disclosures: Physiotherapy Foundation of Canada financial support

Jiang 2011

Methods	Randomised controlled trials
Participants	Country: Taiwan Number randomised: 90 Postrandomisation dropouts: 3 Mean age: 48 years Females: information not available Inclusion criteria: • Clinical idiopathic CTS with repeated pain for > 1 year Exclusion criteria: • Medical histories of systemic disease

Jiang 2011 (*Continued*)

	• Previous surgery • Other treatments such as anti-inflammatory medicine, acupuncture, and physical therapy
Interventions	Group 1: LLLT (n = 45) Group 2: placebo (n = 43) Intervention: painless light PL-830 laser (Advanced Chips & Products Corp., USA) with wavelength 830 nm, output frequency 10 Hz, mean power 60 mW (2 × 30 mW), treatment dosage 9.7 J/cm^2. 2 diode lasers emitted laser beam (irradiated area 370 mm^2) on palm side of wrist (between the pisiform and navicular bones). LLLT executed for 10 min, 5 times per week for 2 weeks Comparator: placebo laser
Outcomes	VAS, SSS, NCS (sensory latency, motor latency), Phalen's test, Tinel's sign
Notes	Short-term follow-up (< 3 months)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: method of randomisation not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: authors stated blinding but no information available on method of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the four assessments, pain, symptoms, neurological signs and NCS were blind to one evaluator."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: postrandomisation dropouts
Selective reporting (reporting bias)	High risk	Comment: SSS reported but FSS not reported. No protocol or trial registry entry identified
Other bias	Low risk	Quote: "Financial support from the president of the national Taiwan university… also supported in part by the national science council"

Lazovic 2014

Methods	Randomised controlled trial
Participants	Country: Serbia Number randomised: 79 Postrandomisation dropouts: 0 Mean age: 52 years Females: 70 (89%) Inclusion criteria: • Clinical and electrophysiological evidence of CTS • Aged > 18 years Exclusion criteria: • Severe CTS on NCS (CMAP < 3.8 mV or severe reduction of EMG interference pattern or denervation, or both) • Thenar atrophy • Severe pain intensity > 7 based on VAS
Interventions	Group 1: LLLT (n = 40) Group 2: placebo (n = 39) Intervention: aluminium-gallium-arsenide diode laser (Medicolaser 637) wavelength 780 nm, power output 30 mW continuous wave, array 0.785 cm^2, power density 38.2 mW/cm^2 applied in contact with 4 points perpendicularly on skin on volar side of wrist over carpal tunnel area for 90 s/point (2.7 J, 3.4 J/cm^2/point). Total of 20 treatments with following schedule: 10 treatments once per day, 5 days per week for 2 weeks, followed by 10 treatments every other day for 3 weeks Comparator: placebo laser
Outcomes	VAS (pain) (categorical: mild/moderate/severe), Tinel's sign, NCS (motor latency, sensory velocity)
Notes	Short-term follow-up (< 3 months)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Comment: randomly allocated using numbered envelopes
Allocation concealment (selection bias)	Low risk	Quote: "allocated using the numbered envelopes method"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both physicians, as well as the participants and the staff who applied the procedures, were unaware of the therapy"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "NCS evaluations were performed by another physician...unaware of the therapy"

Lazovic 2014 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: some important outcomes which would generally be assessed were not reported. No protocol or trial registry entry identified
Other bias	Low risk	Quote: "no competing financial interests exist"

Lucantoni 1992

Methods	Randomised controlled trial.
Participants	Country: Italy Number randomised: 40 Postrandomisation dropouts: 0 Mean age: information not available Females: 40 (100%) Inclusion criteria: • Clinical and electrophysiological evidence of bilateral CTS • Aged 40-60 years • Female Exclusion criteria: • Secondary forms of CTS • Metabolic/rheumatological disease • Median nerve sensorimotor deficit • Distal latency values 6 ms
Interventions	Group 1: LLLT (n = 20) Group 2: steroid injection (n = 20) Intervention: helium-neon laser, frequency 3000 Hz Comparator: methylprednisolone acetate 20 mg
Outcomes	Improvement in pain and paraesthesia (0-3 scale), NCS (motor latency and sensory latency)
Notes	Short-term (< 3 months) and long-term (6 months) follow-up

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available

Lucantoni 1992 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: blinding of participants to treatment not performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: some important outcomes which would generally be assessed were not reported. No protocol or trial registry entry identified
Other bias	Unclear risk	Comment: information not available

Pratelli 2015

Methods	Randomised controlled trial
Participants	Country: Italy Number randomised: 42 Postrandomisation dropouts: 0 Mean age: 54 years Females: 29 (69%) Inclusion criteria: • Clinical and electrophysiological evidence of CTS Exclusion criteria: • Congenital coagulopathy, anticoagulant therapy • Previous treatments < 3 months • Only weakness symptoms • Concomitant tumours • Systemic neurological and rheumatological pathologies
Interventions	Group 1: LLLT (n = information not available, 35 hands) Group 2: fascial manipulation (n = information not available, 35 hands) Intervention: M300 level laser with wavelength of 780-830 nm, power output 1000-3000 mW Comparator: 3 sessions of fascial manipulation for 45 min once per week for 3 weeks. Technique involved deep friction over specific points (centre of co-ordinations or centre of fusions) selected by a clinical examination that involved specific movement and palpatory verification. Therapist used elbow and knuckles to create friction on identified points. Each point had surface area < 2 cm^2. Friction maintained for mean time of 3 min (range: 2-4 min) as indicated by technique. Number of points treated in each session 4-8 (mean 6)
Outcomes	VAS, SSS, FSS

Pratelli 2015 (*Continued*)

Notes	Short-term follow-up (< 3 months)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "The investigator flipped a coin to determine whether the participant should go into group A or B" Comment: inadequate method of randomisation
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Only one degree of blinding was possible due to the different modality of treatment" Comment: participants not blinded to treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All participants were evaluated by physician P. C. who was blinded from the original patient group"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: all important outcomes which would generally be assessed were reported. No protocol or trial registry entry identified
Other bias	Unclear risk	Comment: information not available

Rayegani 2013

Methods	Randomised controlled trial
Participants	Country: Iran Number randomised: 50 Postrandomisation dropouts: 0 Mean age: 49 years Females: information not available Inclusion criteria: • Presence of pain/paraesthesia in distribution of median nerve • Positive clinical provocative test for CTS (Tinel's test, Phalen's test) • Electrophysiological evidence of mild or moderate median nerve lesion at wrist (mild: sensory nerve latency > 3.5 ms at third digit; moderate: sensory nerve latency > 3.5 ms at third digit and median motor latency > 4.2 ms) Exclusion criteria: • Presence of conditions affecting nerve conduction or abnormal findings in other nerves such as the presence of polyneuropathies, as well as proximal neuropathies affecting nerve trunks, plexus, or cervical roots diagnosed by physical examinations,

Rayegani 2013 (*Continued*)

	and comprehensive electrodiagnostic studies
Interventions	Group 1: LLLT + splinting + vitamin B_6 (n = 18) Group 2: placebo LLLT + splinting vitamin B_6 (n = 15) Group 3: splinting + vitamin B_6 (n = 17) Intervention: Multiwave Locked System indium laser of M1 type, continuous waves with wavelength 880 nm, frequency 1000 Hz. Each session lasted 10 minutes, consisting of radiating dose delivered to 5 points of skin overlying course of median nerve, delivered for 120 seconds at each point along course of median nerve in each hand Hands of participants in all 3 groups were splinted with a static wrist splint fixed in 0° of wrist flexion. Participants instructed to use splint daily Information regarding dose of vitamin B_6 not provided. Comparator: placebo laser
Outcomes	VAS, SSS, FSS, NCS (motor amplitude and latency, sensory amplitude, and latency)
Notes	Short-term follow-up (< 3 months)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "They were randomly assigned to one of three treatment groups by means of the random number table"
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Patients were blinded to the treatment used in Laser and Sham Laser group;" "This study was designed as single blinded controlled." Comment: personnel not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: outcome assessors not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: all important outcomes which would generally be assessed were reported. No protocol or trial registry entry identified
Other bias	Unclear risk	Comment: information not available

Rodrigues 2013

Methods	Randomised controlled trial
Participants	Country: Cuba Number randomised: 42 Postrandomisation dropouts: 0 Mean age: 50-59 years Females: 40 (95%) Inclusion criteria: • Clinical evidence of CTS • < 6 months' duration Exclusion criteria: • Conditions that contraindicated rehabilitation treatment or administration of NSAIDs, or both
Interventions	Group 1: LLLT (n = 21) Group 2: splint + NSAIDs (n = 21) Intervention: Expert laserterapia (Physiomed), power output 700 mW, wavelength 785 nm, treatment dosage 6 J/cm^2 Comparator: postural hand splint in neutral wrist + NSAIDs
Outcomes	Pain, NCS, neurophysiological injury (as defined by study authors)
Notes	Short-term follow-up (< 3 months)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available
Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: blinding of participants to treatment not performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: some important outcomes which would generally be assessed were not reported. No protocol or trial registry entry identified
Other bias	Unclear risk	Comment: information not available

Saeed 2012

Methods	Randomised controlled trial
Participants	Country: Pakistan Number randomised: 100 Postrandomisation dropouts: 0 Mean age: 36 years Females: 55 (55%) Inclusion criteria: • Unilateral CTS • > 4 months' duration • No other compressive neuropathy or general neuropathy on NCS Exclusion criteria: • History of fracture • Steroid injection • Surgical decompression
Interventions	Group 1: LLLT (n = 50) Group 2: ultrasound (n = 50) Intervention: 9 J infrared laser diode (Enraf, Endolaser 830 nm) at 1.8 J/point over wrist Comparator: ultrasound therapy at 1 MHz and intensity 1.0 W/cm^2 with Enraf Sonopuls 492
Outcomes	VAS, SSS
Notes	Short-term follow-up (< 3 months)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Computer generated randomization was done by the statistician..."
Allocation concealment (selection bias)	Low risk	Quote: "...and it was given to the physiotherapy dept in two sets of sealed envelopes."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The staff who assessed the outcomes were different from the staff administering the treatments and they were blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: some important outcomes which would generally be assessed were not reported. No protocol or trial registry entry identified

Saeed 2012 (*Continued*)

Other bias	Unclear risk	Comment: information not available

Shooshtari 2008

Methods	Randomised controlled trial
Participants	Country: Iran Number randomised: 80 Postrandomisation dropouts: 0 Mean age: 48 years Females: 73 (91%) Inclusion criteria: • Clinical and electrophysiological evidence of CTS Exclusion criteria: • Trauma to hand or neck • Systemic disease • Pregnancy • Hand oedema • Obesity • Previous carpal bone fracture or surgery • Severe NCS findings
Interventions	Group 1: LLLT (n = 40) Group 2: placebo (n = 40) Intervention: low power laser waves by physiolaser Olympic with multicluster probe (Germany) with wavelength 785 nM and EC Nogier frequencies (4672 Hz and 1168 Hz) in the form of pulse and energy 9-11 J/cm^2 and 400 mw at anterior side of wrist and palm for 15 sessions (5 times per week) Comparator: placebo laser
Outcomes	VAS (pain), grip strength, NCS (motor and sensory latency, sensory nerve conduction velocity)
Notes	Short-term follow-up (< 3 months)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: randomisation method not available
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment method not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available

Shooshtari 2008 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: some important outcomes which would generally be assessed were not reported. No protocol or trial registry entry identified
Other bias	Unclear risk	Vested interest bias information not available

Soltani 2013

Methods	Randomised controlled trial
Participants	Country: Turkey Number randomised: 33 Postrandomisation dropouts: 0 Mean age: 47 years Females: 28 (85%) Inclusion criteria: • Clinical and electrophysiological evidence of CTS Exclusion criteria: • Secondary CTS • Previous steroid injection • Previous LLLT • Severe symptoms • Willing to undergo surgery
Interventions	Group 1: LLLT (n = 16) Group 2: steroid injection (n = 17) Intervention: low potent laser characterised with amplitude 775 nm, frequency 6500 Hz and intensity 20 J/cm^2 Comparator: hydrocortisone 50 mg
Outcomes	VAS, NCS (motor and sensory distal latency, motor and sensory amplitude)
Notes	Short-term follow-up (< 3 months)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly assigned to the groups at the coordination room of the research center according to a computer-generated randomization list."

Soltani 2013 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Comment: information not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: participants not blinded to treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Outcome assessments were performed by blinded study physicians."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Unclear risk	Comment: some important outcomes which would generally be assessed were not reported. No protocol or trial registry entry identified
Other bias	Unclear risk	Comment: information not available

Tascioglu 2012

Methods	Randomised controlled trial
Participants	Country: Turkey Number randomised: 60 Postrandomisation dropouts: 0 Mean age: 50 years Females: 46 (76%) Inclusion criteria: • Clinical and electrophysiological evidence of CTS • < 6 months' duration Exclusion criteria: • Wrist injection • Surgery or fracture • Accompanying conditions that mimic CTS or interfere with its evaluation • Underlying disorders associated with CTS • Anatomical variation of the median nerve • Previous physiotherapy
Interventions	Group 1: LLLT, dosage 90 J (n = 20) Group 2: LLLT, dosage 45 J (n = 20) Group 3: placebo (n = 20) Intervention: aluminium-gallium-arsenide diode laser device (Endolaser 476, Enraf-Nonius, Netherlands) with power output 50 mW and wavelength 830 nm. Diameter of laser beam at treatment point 1 mm. Laser set to deliver continuous form of energy. A total of 5 points across median nerve trace irradiated with laser probe. Participants in group 1 received irradiation at each point of skin overlying median nerve on volar side at the wrist. A 2-min irradiation at each point (total 10 min) was considered as 1

Tascioglu 2012 (*Continued*)

	irradiation at each point. Dose per tender joint 1.2 J, total dose per treatment 6 J, and accumulated dose for 15 treatments 90 J. Group 2 received 3 J dose per treatment (45 J total) Comparator: placebo laser Groups 1 and 2 were combined for further statistical analysis
Outcomes	VAS, SSS, FSS, grip strength, motor distal latency and velocity, sensory velocity, cross-sectional ultrasound scan findings
Notes	Short-term follow-up (< 3 months)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned to three groups by a secure system of numbered 1-3 opaque closed envelopes. The physician who assigned the patients was blinded to the treatment they would receive."
Allocation concealment (selection bias)	Low risk	Quote: "randomly assigned to three groups by a secure system of numbered 1-3 opaque closed envelopes. The physician who assigned the patients was blinded to the treatment they would receive."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information regarding blinding of participants not available
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "a blinded physician unaware of the treatment allocation performed the clinical assessments at baseline and at the end of therapy."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: all important outcomes were reported. No protocol or trial registry entry identified
Other bias	Unclear risk	Vested interest bias information unavailable

Tikiz 2013

Methods	Randomised controlled trial
Participants	Country: Turkey. Number randomised: 60 Postrandomisation dropouts: 8

	Mean age: 48 years Females: 46 (88%) Inclusion criteria: • Clinical evidence of CTS • > 6 weeks' duration Exclusion criteria: • CTS predisposed by aetiological factors • NSAIDs • Steroid injection or physiotherapy in previous month • Cervical radiculopathy • Polyneuropathy • Proximal neuropathy of the median nerve • Ulnar neuropathy
Interventions	Group 1: ultrasound (n = 14) Group 2: ultrasound placebo (n = 12) Group 3: LLLT (n = 13) Group 4: LLLT placebo (n = 13) Intervention LLLT: aluminium-gallium-arsenide laser "Endolaser 476 Enraf-Nonus, Netherlands" with power output 30 mW, wavelength 830 nm Intervention ultrasound: pulsed ultrasound (Sonicate 730, Mettler Electronics, USA) at frequency 3 MHz, dosage 1 W/cm^2 Comparator: placebo laser Comparator 2: placebo ultrasound
Outcomes	VAS, numbness VAS, hand grip strength, SSS, FSS, NCS (motor distal latency and velocity, sensory velocity), cross-sectional ultrasound scan findings
Notes	Short-term (< 3 month) and long-term (12 month)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Quote: "Arrivals by order of 1, 2, 3, 4 was given to a group, then again..." Comment: inappropriate randomisation method
Allocation concealment (selection bias)	High risk	Quote: "Arrivals by order of 1, 2, 3, 4 was given to a group, then again..." Comment: inappropriate randomisation method
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information unavailable
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information unavailable

Tikiz 2013 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all important outcomes were reported
Selective reporting (reporting bias)	Unclear risk	Comment: all NCS outcomes that would usually be reported were not reported. Important outcome measures otherwise were reported. No protocol or trial registry entry identified
Other bias	Low risk	Quote: "authors have not reported any conflict of interest."

CMAP: compound muscle action potential; CTS: carpal tunnel syndrome; EMG: electromyography; FSS: Functional Status Scale; LLLT: low-level laser therapy; n: number of participants; NCS; nerve conduction studies; NSAID: non-steroidal anti-inflammatory drug; SSS: Symptom Severity Score; VAS: visual analogue score.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Barbosa 2016	LLLT + splint vs splint alone (no placebo LLLT)
Branco 1999	LLLT + TENS or acupuncture
Kotb 2014	LLLT + splint + ultrasound vs splint + steroid injection
Montes-Molina 2011	Included participants with a history of previous surgery for CTS
Naeser 2002	Included participants with a history of previous surgery for CTS
Padua 1999	Not a randomised controlled trial
Tamam 2012	Paper initially stated it studied 56 people who were randomised to 2 groups of 18. The remaining participants were not discussed. Further information not available. We contacted trial authors for further information; however, this was not provided. Therefore, insufficient information to assess eligibility as type of participants not clearly described
Yagci 2009	LLLT + splint vs splint alone (no placebo LLLT)

CTS: carpal tunnel syndrome; LLLT: low level laser therapy; TENS: transcutaneous electrical nerve stimulation.

DATA AND ANALYSES

Comparison 1. Low-level laser therapy (LLLT) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptom Severity Score, short term (≤ 3 months)	7	327	Mean Difference (IV, Random, 95% CI)	-0.36 [-0.78, 0.06]
2 Functional Status Scale	5	159	Mean Difference (IV, Random, 95% CI)	-0.56 [-1.03, -0.09]
3 VAS pain	7	392	Mean Difference (IV, Random, 95% CI)	-1.47 [-2.36, -0.58]
4 Grip strength (kg)	5	286	Mean Difference (IV, Random, 95% CI)	2.58 [1.22, 3.95]
5 Finger-pinch strength (kg)	2	121	Mean Difference (IV, Random, 95% CI)	0.94 [0.43, 1.44]
6 Motor nerve latency (ms)	7	446	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.16, -0.03]
7 Sensory nerve latency (ms)	5	307	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.15, -0.06]
8 Sensory nerve velocity (m/s)	2	139	Mean Difference (IV, Random, 95% CI)	1.48 [-5.68, 8.65]

Comparison 2. Low-level laser therapy (LLLT) versus ultrasound

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptom Severity Score	2	127	Mean Difference (IV, Random, 95% CI)	0.43 [0.36, 0.50]
2 Functional Status Scale	2	127	Mean Difference (IV, Random, 95% CI)	0.35 [0.29, 0.41]
3 Visual analogue score	3	177	Mean Difference (IV, Random, 95% CI)	2.81 [1.21, 4.40]
4 Grip strength (kg)	2	77	Mean Difference (IV, Random, 95% CI)	-0.89 [-4.30, 2.52]
5 Motor nerve latency (ms)	3	177	Mean Difference (IV, Random, 95% CI)	0.61 [0.27, 0.95]
6 Sensory nerve latency (ms)	3	177	Mean Difference (IV, Random, 95% CI)	0.43 [-0.01, 0.87]
7 Motor amplitude (mV)	2	77	Mean Difference (IV, Random, 95% CI)	-1.90 [-3.63, -0.18]
8 Sensory latency - preanalysis (ms)	3		Mean Difference (Random, 95% CI)	0.43 [-0.01, 0.87]
9 Sensory latency, intracluster correlation coefficient 1.00 (ms)	3		Mean Difference (Random, 95% CI)	0.47 [0.39, 0.55]

Comparison 3. Low-level laser therapy (LLLT) versus steroid injection

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Motor latency (ms)	2	73	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.39, 0.30]

Analysis 1.1. Comparison 1 Low-level laser therapy (LLLT) versus placebo, Outcome 1 Symptom Severity Score, short term (≤ 3 months).

Review: Low-level laser therapy for carpal tunnel syndrome

Comparison: 1 Low-level laser therapy (LLLT) versus placebo

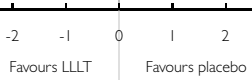
Outcome: 1 Symptom Severity Score, short term (≤ 3 months)

Study or subgroup	Favours LLLT N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Chang 2008	20	1.76 (0.057)	20	2.61 (0.077)		16.6 %	-0.85 [-0.89, -0.81]
Ekim 2007	10	1.64 (0.64)	9	1.91 (0.364)		13.8 %	-0.27 [-0.73, 0.19]
Evcik 2007	41	2.15 (0.18)	40	2.15 (0.2)		16.5 %	0.0 [-0.08, 0.08]
Irvine 2004	7	1.9 (0.6)	8	1.9 (0.4)		13.2 %	0.0 [-0.52, 0.52]
Jiang 2011	45	-0.83 (0.32)	42	-0.18 (0.49)		16.1 %	-0.65 [-0.83, -0.47]
Tascioglu 2012	40	1.67 (0.631)	20	1.85 (0.656)		14.9 %	-0.18 [-0.53, 0.17]
Tikiz 2013	13	2.3 (1.1)	12	2.9 (1.3)		9.0 %	-0.60 [-1.55, 0.35]
Total (95% CI)	**176**		**151**			**100.0 %**	**-0.36 [-0.78, 0.06]**

Heterogeneity: $Tau^2 = 0.28$; $Chi^2 = 338.11$, df = 6 (P<0.00001); $I^2 = 98\%$

Test for overall effect: Z = 1.70 (P = 0.090)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Low-level laser therapy (LLLT) versus placebo, Outcome 2 Functional Status Scale.

Review: Low-level laser therapy for carpal tunnel syndrome

Comparison: 1 Low-level laser therapy (LLLT) versus placebo

Outcome: 2 Functional Status Scale

Study or subgroup	LLLT N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Chang 2008 (1)	20	1.38 (0.054)	20	2.45 (0.1275)		25.5 %	-1.07 [-1.13, -1.01]
Tikiz 2013	13	2.2 (1)	12	3.2 (1)		15.0 %	-1.00 [-1.78, -0.22]
Tascioglu 2012	40	1.72 (0.598)	20	2.16 (0.611)		22.9 %	-0.44 [-0.77, -0.11]
Ekim 2007	10	1.75 (0.525)	9	2.13 (0.375)		21.5 %	-0.38 [-0.78, 0.03]
Irvine 2004	7	1.8 (0.9)	8	1.5 (0.6)		15.0 %	0.30 [-0.49, 1.09]
Total (95% CI)	**90**		**69**			**100.0 %**	**-0.56 [-1.03, -0.09]**

Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 35.22$, df = 4 ($P<0.00001$); $I^2 = 89\%$

Test for overall effect: Z = 2.32 (P = 0.020)

Test for subgroup differences: Not applicable

(1) Forest plot of LLLT versus placebo showing lower FSS in LLLT group

Analysis 1.3. Comparison 1 Low-level laser therapy (LLLT) versus placebo, Outcome 3 VAS pain.

Review: Low-level laser therapy for carpal tunnel syndrome

Comparison: 1 Low-level laser therapy (LLLT) versus placebo

Outcome: 3 VAS pain

Study or subgroup	Favours LLLT N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Chang 2008	20	3 (4.05)	20	6 (5)		6.5 %	-3.00 [-5.82, -0.18]
Ekim 2007	10	3.3 (0.9)	9	4.3 (0.6)		16.5 %	-1.00 [-1.68, -0.32]
Evcik 2007	41	2.28 (0.76)	40	2.88 (2)		16.6 %	-0.60 [-1.26, 0.06]
Jiang 2011 (1)	45	-2.92 (1.61)	42	-1.04 (1.12)		17.0 %	-1.88 [-2.46, -1.30]
Shooshtari 2008	40	4.98 (0.12)	40	7.62 (0.4)		18.2 %	-2.64 [-2.77, -2.51]
Tascioglu 2012	40	3.93 (1.82)	20	4.55 (1.39)		15.8 %	-0.62 [-1.45, 0.21]
Tikiz 2013	13	3.18 (2.7)	12	4.37 (2.49)		9.4 %	-1.19 [-3.22, 0.84]
Total (95% CI)	**209**		**183**			**100.0 %**	**-1.47 [-2.36, -0.58]**

Heterogeneity: $Tau^2 = 1.13$; $Chi^2 = 79.64$, df = 6 (P<0.00001); $I^2 = 92\%$

Test for overall effect: Z = 3.23 (P = 0.0013)

Test for subgroup differences: Not applicable

(1) Forest plot of LLLT versus placebo showing lower VAS pain in LLLT group

Analysis 1.4. Comparison 1 Low-level laser therapy (LLLT) versus placebo, Outcome 4 Grip strength (kg).

Review: Low-level laser therapy for carpal tunnel syndrome

Comparison: 1 Low-level laser therapy (LLLT) versus placebo

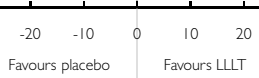
Outcome: 4 Grip strength (kg)

Study or subgroup	LLLT N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Chang 2008	20	21.19 (4.12)	20	17.38 (3.56)		32.8 %	3.81 [1.42, 6.20]
Evcik 2007 (1)	41	22.8 (6.9)	40	19.6 (7.3)		19.5 %	3.20 [0.11, 6.29]
Shooshtari 2008 (2)	40	22.86 (5.13)	40	21.52 (6.05)		30.9 %	1.34 [-1.12, 3.80]
Tascioglu 2012	40	25.23 (7.43)	20	24.48 (7.43)		11.7 %	0.75 [-3.24, 4.74]
Tikiz 2013	13	18.3 (9.4)	12	14.2 (5.9)		5.0 %	4.10 [-2.00, 10.20]
Total (95% CI)	**154**		**132**			**100.0 %**	**2.58 [1.22, 3.95]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.20$, df = 4 (P = 0.53); $I^2 = 0.0\%$

Test for overall effect: Z = 3.70 (P = 0.00021)

Test for subgroup differences: Not applicable



(1) Forest plot of LLLT versus placebo showing higher grip strength in LLLT group

(2) Forest plot of LLLT versus placebo showing higher grip strength in LLLT group

Analysis 1.5. Comparison 1 Low-level laser therapy (LLLT) versus placebo, Outcome 5 Finger-pinch strength (kg).

Review: Low-level laser therapy for carpal tunnel syndrome

Comparison: 1 Low-level laser therapy (LLLT) versus placebo

Outcome: 5 Finger-pinch strength (kg)

Study or subgroup	LLLT N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Chang 2008 (1)	20	5.33 (1.33)	20	4.35 (1.09)		44.5 %	0.98 [0.23, 1.73]
Evcik 2007 (2)	41	5.7 (1.6)	40	4.8 (1.5)		55.5 %	0.90 [0.22, 1.58]
Total (95% CI)	**61**		**60**			**100.0 %**	**0.94 [0.43, 1.44]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.02$, df = 1 (P = 0.88); $I^2 = 0.0\%$

Test for overall effect: Z = 3.65 (P = 0.00027)

Test for subgroup differences: Not applicable

(1) Forest plot of LLLT versus placebo showing higher pinch strength in LLLT group

(2) Forest plot of LLLT versus placebo showing higher pinch strength in LLLT group

Analysis 1.6. Comparison 1 Low-level laser therapy (LLLT) versus placebo, Outcome 6 Motor nerve latency (ms).

Review: Low-level laser therapy for carpal tunnel syndrome

Comparison: 1 Low-level laser therapy (LLLT) versus placebo

Outcome: 6 Motor nerve latency (ms)

Study or subgroup	LLLT N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Chang 2008	20	3.87 (0.3)	20	4.1 (0.21)		15.3 %	-0.23 [-0.39, -0.07]
Ekim 2007	10	3.3 (0.7)	9	3.1 (0.5)		1.3 %	0.20 [-0.34, 0.74]
Evcik 2007 (1)	41	4.1 (0.7)	40	4.2 (1.08)		2.5 %	-0.10 [-0.50, 0.30]
Jiang 2011	45	-0.2 (0.2)	42	-0.12 (0.15)		71.8 %	-0.08 [-0.15, -0.01]
Lazovic 2014	40	4.69 (1.51)	39	4.99 (2.01)		0.6 %	-0.30 [-1.09, 0.49]
Shooshtari 2008	40	3.94 (0.51)	40	3.94 (0.52)		7.7 %	0.0 [-0.23, 0.23]
Tascioglu 2012	40	4.09 (1.38)	20	4.05 (1.35)		0.7 %	0.04 [-0.69, 0.77]
Total (95% CI)	**236**		**210**			**100.0 %**	**-0.09 [-0.16, -0.03]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.08$, df = 6 (P = 0.53); $I^2 = 0.0\%$

Test for overall effect: Z = 2.94 (P = 0.0033)

Test for subgroup differences: Not applicable

(1) Forest plot of LLLT versus placebo showing lower motor nerve latency in LLLT group

Analysis 1.7. Comparison 1 Low-level laser therapy (LLLT) versus placebo, Outcome 7 Sensory nerve latency (ms).

Review: Low-level laser therapy for carpal tunnel syndrome

Comparison: 1 Low-level laser therapy (LLLT) versus placebo

Outcome: 7 Sensory nerve latency (ms)

Study or subgroup	LLLT N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Chang 2008 (1)	20	3.67 (0.21)	20	3.8 (0.11)		17.0 %	-0.13 [-0.23, -0.03]
Ekim 2007 (2)	10	1.9 (0.4)	9	1.8 (0.3)		1.8 %	0.10 [-0.22, 0.42]
Evcik 2007 (3)	41	3 (0.5)	40	3.1 (0.6)		3.2 %	-0.10 [-0.34, 0.14]
Jiang 2011	45	-0.18 (0.13)	42	-0.07 (0.11)		71.9 %	-0.11 [-0.16, -0.06]
Shooshtari 2008	40	3.86 (0.4)	40	3.9 (0.39)		6.1 %	-0.04 [-0.21, 0.13]
Total (95% CI)	**156**		**151**			**100.0 %**	**-0.10 [-0.15, -0.06]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.42$, df = 4 (P = 0.66); $I^2 = 0.0\%$

Test for overall effect: Z = 4.80 (P < 0.00001)

Test for subgroup differences: Not applicable

(1) Forest plot of LLLT versus placebo showing lower sensory nerve latency in LLLT group

(2) Forest plot of LLLT versus placebo showing lower sensory nerve latency in LLLT group

(3) Forest plot of LLLT versus placebo showing lower sensory nerve latency in LLLT group

Analysis 1.8. Comparison 1 Low-level laser therapy (LLLT) versus placebo, Outcome 8 Sensory nerve velocity (m/s).

Review: Low-level laser therapy for carpal tunnel syndrome

Comparison: 1 Low-level laser therapy (LLLT) versus placebo

Outcome: 8 Sensory nerve velocity (m/s)

Study or subgroup	LLLT N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Lazovic 2014 (1)	40	41.81 (10.12)	39	36.56 (9.79)		48.5 %	5.25 [0.86, 9.64]
Tascioglu 2012	40	33.63 (7.48)	20	35.69 (6.34)		51.5 %	-2.06 [-5.68, 1.56]
Total (95% CI)	**80**		**59**			**100.0 %**	**1.48 [-5.68, 8.65]**

Heterogeneity: $Tau^2 = 22.50$; $Chi^2 = 6.34$, df = 1 (P = 0.01); $I^2 = 84\%$

Test for overall effect: Z = 0.41 (P = 0.68)

Test for subgroup differences: Not applicable

(1) Forest plot of LLLT versus placebo showing no significant difference of sensory nerve velocity between LLLT and placebo

Analysis 2.1. Comparison 2 Low-level laser therapy (LLLT) versus ultrasound, Outcome 1 Symptom Severity Score.

Review: Low-level laser therapy for carpal tunnel syndrome

Comparison: 2 Low-level laser therapy (LLLT) versus ultrasound

Outcome: 1 Symptom Severity Score

Study or subgroup	LLT N	Mean(SD)	Ultrasound N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Saeed 2012 (1)	50	-0.44 (0.18)	50	-0.87 (0.18)		98.9 %	0.43 [0.36, 0.50]
Tikiz 2013	13	2.3 (1.1)	14	1.8 (0.6)		1.1 %	0.50 [-0.18, 1.18]
Total (95% CI)	**63**		**64**			**100.0 %**	**0.43 [0.36, 0.50]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.04$, df = 1 (P = 0.84); $I^2 = 0.0\%$

Test for overall effect: Z = 12.03 (P < 0.00001)

Test for subgroup differences: Not applicable

(1) Forest plot of LLLT versus placebo showing higher SSS in LLT group

Analysis 2.2. Comparison 2 Low-level laser therapy (LLLT) versus ultrasound, Outcome 2 Functional Status Scale.

Review: Low-level laser therapy for carpal tunnel syndrome

Comparison: 2 Low-level laser therapy (LLLT) versus ultrasound

Outcome: 2 Functional Status Scale

Study or subgroup	LLLT		Ultrasound		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Saeed 2012 (1)	50	-0.4 (0.17)	50	-0.75 (0.12)		99.3 %	0.35 [0.29, 0.41]
Tikiz 2013 (2)	13	2.2 (1)	14	1.9 (0.8)		0.7 %	0.30 [-0.39, 0.99]
Total (95% CI)	**63**		**64**			**100.0 %**	**0.35 [0.29, 0.41]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.02$, df = 1 (P = 0.89); $I^2 = 0.0\%$

Test for overall effect: Z = 11.92 (P < 0.00001)

Test for subgroup differences: Not applicable

(1) Forest plot of LLLT versus USS showing higher FSS (worse function) in LLLT group

(2) Forest plot of LLLT versus placebo showing higher FSS (worse function) in LLLT group

Analysis 2.3. Comparison 2 Low-level laser therapy (LLLT) versus ultrasound, Outcome 3 Visual analogue score.

Review: Low-level laser therapy for carpal tunnel syndrome

Comparison: 2 Low-level laser therapy (LLLT) versus ultrasound

Outcome: 3 Visual analogue score

Study or subgroup	LLLT N	Mean(SD)	Ultrasound N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Bakhtiary 2004 (1)	25	-2 (1.3)	25	-6.3 (1.6)		36.0 %	4.30 [3.49, 5.11]
Saeed 2012	50	-2.6 (1.07)	50	-4.9 (1.46)		38.2 %	2.30 [1.80, 2.80]
Tikiz 2013	13	3.18 (2.7)	14	1.71 (2.16)		25.8 %	1.47 [-0.38, 3.32]
Total (95% CI)	**88**		**89**			**100.0 %**	**2.81 [1.21, 4.40]**

Heterogeneity: $Tau^2 = 1.67$; $Chi^2 = 19.03$, df = 2 (P = 0.00007); $I^2 = 89\%$

Test for overall effect: Z = 3.45 (P = 0.00057)

Test for subgroup differences: Not applicable

(1) Forest plot of LLLT versus USS showing higher VAS (pain) in LLLT group

Analysis 2.4. Comparison 2 Low-level laser therapy (LLLT) versus ultrasound, Outcome 4 Grip strength (kg).

Review: Low-level laser therapy for carpal tunnel syndrome

Comparison: 2 Low-level laser therapy (LLLT) versus ultrasound

Outcome: 4 Grip strength (kg)

Study or subgroup	LLLT N	Mean(SD)	Ultrasound N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Bakhtiary 2004 (1)	25	2.16 (1.88)	25	4 (2.19)		77.1 %	-1.84 [-2.97, -0.71]
Tikiz 2013	13	18.3 (9.4)	14	16 (6.3)		22.9 %	2.30 [-3.78, 8.38]
Total (95% CI)	**38**		**39**			**100.0 %**	**-0.89 [-4.30, 2.52]**

Heterogeneity: $Tau^2 = 3.59$; $Chi^2 = 1.72$, df = 1 (P = 0.19); $I^2 = 42\%$

Test for overall effect: Z = 0.51 (P = 0.61)

Test for subgroup differences: Not applicable

(1) Forest plot of LLLT versus USS showing no significant difference of grip strength between LLLT and USS group

Analysis 2.5. Comparison 2 Low-level laser therapy (LLLT) versus ultrasound, Outcome 5 Motor nerve latency (ms).

Review: Low-level laser therapy for carpal tunnel syndrome

Comparison: 2 Low-level laser therapy (LLLT) versus ultrasound

Outcome: 5 Motor nerve latency (ms)

Study or subgroup	LLLT N	Mean(SD)	Ultrasound N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Bakhtiary 2004 (1)	25	-0.2 (0.2)	25	-1.1 (0.5)		41.1 %	0.90 [0.69, 1.11]
Saeed 2012	50	-0.18 (0.13)	50	-0.8 (0.23)		47.8 %	0.62 [0.55, 0.69]
Tikiz 2013	13	4.33 (0.8)	14	4.8 (1.5)		11.1 %	-0.47 [-1.37, 0.43]
Total (95% CI)	**88**		**89**			**100.0 %**	**0.61 [0.27, 0.95]**

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 11.97$, df = 2 (P = 0.003); $I^2 = 83\%$

Test for overall effect: Z = 3.55 (P = 0.00039)

Test for subgroup differences: Not applicable

(1) Forest plot of LLLT versus USS showing motor nerve latency in LLLT group

Analysis 2.6. Comparison 2 Low-level laser therapy (LLLT) versus ultrasound, Outcome 6 Sensory nerve latency (ms).

Review: Low-level laser therapy for carpal tunnel syndrome

Comparison: 2 Low-level laser therapy (LLLT) versus ultrasound

Outcome: 6 Sensory nerve latency (ms)

Study or subgroup	LLLT		Ultrasound		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Bakhtiary 2004	25	0.1 (1.1)	25	-0.8 (1)		27.0 %	0.90 [0.32, 1.48]
Saeed 2012 (1)	50	-0.07 (0.07)	50	-0.54 (0.28)		50.4 %	0.47 [0.39, 0.55]
Tikiz 2013	13	3.7 (0.7)	14	3.9 (1.1)		22.6 %	-0.20 [-0.89, 0.49]
Total (95% CI)	**88**		**89**			**100.0 %**	**0.43 [-0.01, 0.87]**

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 5.71$, df = 2 (P = 0.06); $I^2 = 65\%$

Test for overall effect: Z = 1.94 (P = 0.053)

Test for subgroup differences: Not applicable

(1) Forest plot of LLLT versus USS showing no significant difference of sensory nerve latency between LLLT and USS group

Analysis 2.7. Comparison 2 Low-level laser therapy (LLLT) versus ultrasound, Outcome 7 Motor amplitude (mV).

Review: Low-level laser therapy for carpal tunnel syndrome

Comparison: 2 Low-level laser therapy (LLLT) versus ultrasound

Outcome: 7 Motor amplitude (mV)

Study or subgroup	LLLT N	Mean(SD)	Ultrasound N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Bakhtiary 2004	25	1.1 (2.9)	25	3.6 (1.5)		68.6 %	-2.50 [-3.78, -1.22]
Tikiz 2013 (1)	13	9.1 (3.9)	14	9.7 (2.9)		31.4 %	-0.60 [-3.21, 2.01]
Total (95% CI)	**38**		**39**			**100.0 %**	**-1.90 [-3.63, -0.18]**

Heterogeneity: $Tau^2 = 0.71$; $Chi^2 = 1.64$, df = 1 (P = 0.20); $I^2 = 39\%$

Test for overall effect: Z = 2.16 (P = 0.031)

Test for subgroup differences: Not applicable

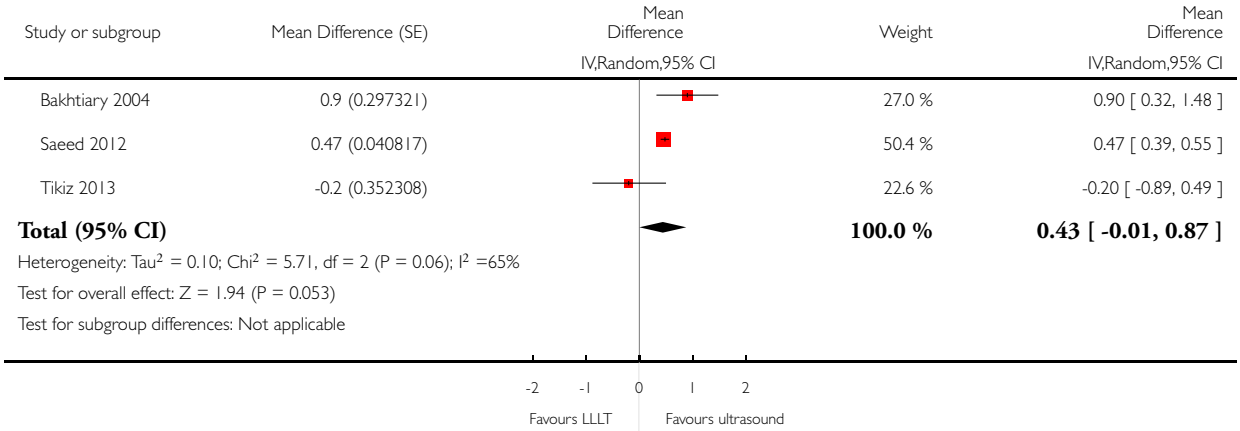
(1) Forest plot of LLLT versus USS showing lower motor amplitude in LLLT group

Analysis 2.8. Comparison 2 Low-level laser therapy (LLLT) versus ultrasound, Outcome 8 Sensory latency - preanalysis (ms).

Review: Low-level laser therapy for carpal tunnel syndrome

Comparison: 2 Low-level laser therapy (LLLT) versus ultrasound

Outcome: 8 Sensory latency - preanalysis (ms)



Analysis 2.9. Comparison 2 Low-level laser therapy (LLLT) versus ultrasound, Outcome 9 Sensory latency, intracluster correlation coefficient 1.00 (ms).

Review: Low-level laser therapy for carpal tunnel syndrome

Comparison: 2 Low-level laser therapy (LLLT) versus ultrasound

Outcome: 9 Sensory latency, intracluster correlation coefficient 1.00 (ms)

Study or subgroup	Mean Difference (SE)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Bakhtiary 2004	0.9 (0.535)		0.6 %	0.90 [-0.15, 1.95]
Saeed 2012	0.47 (0.040817)		99.1 %	0.47 [0.39, 0.55]
Tikiz 2013	-0.2 (0.69)		0.3 %	-0.20 [-1.55, 1.15]
Total (95% CI)			**100.0 %**	**0.47 [0.39, 0.55]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.59$, df = 2 (P = 0.45); $I^2 = 0.0\%$

Test for overall effect: Z = 11.57 (P < 0.00001)

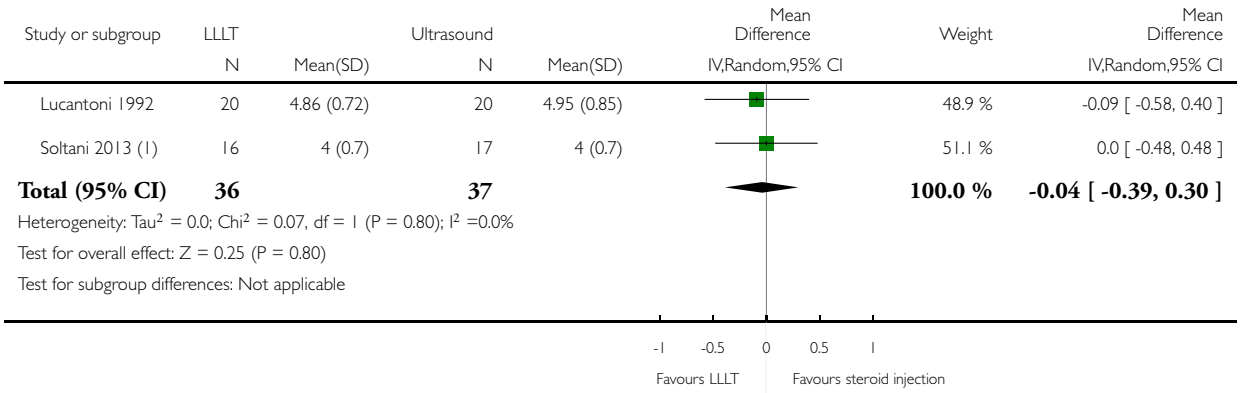
Test for subgroup differences: Not applicable

Analysis 3.1. Comparison 3 Low-level laser therapy (LLLT) versus steroid injection, Outcome 1 Motor latency (ms).

Review: Low-level laser therapy for carpal tunnel syndrome

Comparison: 3 Low-level laser therapy (LLLT) versus steroid injection

Outcome: 1 Motor latency (ms)



(1) Forest plot of LLLT versus steroid injection showing no significant difference of motor latency between LLLT and placebo

APPENDICES

Appendix 1. CENTRAL (Wiley) search strategy

Searched 9 December 2016
#1 “carpal tunnel syndrome”:ti,ab,kw
#2 ((nerve entrapmen* or nerve compression or entrapment neuropath*) and carpal)
#3 #1 OR #2
#4 “low-level light therapy”:ti,ab,kw
#5 “lasers”:ti,ab,kw
#6 laser or low-level or LLLT
#7 #4 OR #5 OR #6
#8 #3 AND #7

Appendix 2. MEDLINE (Pubmed) search strategy

Searched 9 December 2016.
((((((((((carpal tunnel syndrome[Title/Abstract] OR median nerve[Title/Abstract] AND carpal[Title/Abstract])))) OR (((nerve entrapment or nerve compression or entrapment neuropath*) and carpal [tiab]))))) OR carpal tunnel syndrome[MeSH Terms])) AND ((low-level light therapy[MeSH Terms]) OR "lasers"[MeSH Terms])) AND (laser [tiab] OR low-level [tiab]or LLLT [tiab])) AND (((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab])) AND humans [mh]))

Appendix 3. Embase (OvidSP) search strategy

Searched 9 December 2016
1. random* or factorial* or crossover* or cross over* or cross-over* or placebo* or doubl* blind* or singl* blind* or assign* or allocate* or volunteer*.af.
2. exp crossover-procedure/ or exp double-blind procedure/ or exp randomized controlled trial/ or exp single-blind procedure/
3. 1. or 2.
4. low level laser therapy/
5. laser or low-level or LLLT.mp.
6, 4. or 5.
7. carpal tunnel syndrome/
8. (carpal tunnel syndrome or median nerve or ((nerve entrapment or nerve compression or entrapment neuropath*) and carpal)).mp.
9. 7. or 8.
10. 9. and 6. and 3.

Appendix 4. Web of Science Core Collection search strategy

Searched 9 December 2016
(random* OR rct* OR crossover OR masked OR blind* OR placebo* OR meta-analysis OR systematic review* OR meta-analys*) AND (carpal tunnel syndrome OR (("nerve entrapment" or "nerve compression" or "entrapment neuropath*") AND carpal)) AND (low-level light therapy OR lasers OR (laser or low-level or LLLT))

Appendix 5. US National Institutes for Health Clinical Trials Registry search strategy

Searched 9 December 2016
(carpal tunnel syndrome OR (("nerve entrapment" or "nerve compression" or "entrapment neuropath*") and carpal)) AND (low-level light therapy OR lasers OR (laser or low-level or LLLT))

Appendix 6. WHO International Clinical Trials Registry Platform search strategy

Searched 9 December 2016
(carpal tunnel syndrome OR (("nerve entrapment" or "nerve compression" or "entrapment neuropath*") and carpal)) AND (low-level light therapy OR lasers OR (laser or low-level or LLLT))

CONTRIBUTIONS OF AUTHORS

IR: designed review; developed search strategy; undertook search of studies; screened search results; organised retrieval of papers; screened retrieved papers against inclusion/exclusion criteria; appraised risk of bias of papers; extracted data from papers; wrote to study investigators for additional information; summarised risk of bias of studies; compiled summary of comparisons, tables of included, excluded, awaiting and ongoing studies; entered data into Review Manager 5; performed analysis of data; interpreted findings; wrote review.

HS: screened search results; screened retrieved papers against inclusion/exclusion criteria; appraised risk of bias of papers; extracted data from papers; checked data entered into Review Manager 5 by IR, summarised risk of bias of studies.

HR: appraised risk of bias of papers; extracted data from papers; summarised risk of bias of studies.

KSG: advised on protocol, review process, search strategies, and data analysis; contributed to writing of review.

DECLARATIONS OF INTEREST

IAR: none known.

HS: none known.

HR: none known.

KSG: none known.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The random-effects model was adopted for all outcomes as the more conservative effects model, regardless of heterogeneity. We expressed results for continuous outcomes as mean differences with 95% confidence intervals where trials used the same scale, as opposed to standardised mean differences for all outcomes. Cochrane Neuromuscular states preference within published guidance for one primary outcome and up to five secondary outcome measures. As such, primary and secondary outcomes were altered to comply with this; however, all outcomes from the initial protocol have been included within the text to avoid selective reporting bias.

The protocol for the review stated that all outcomes would be included in a 'Summary of findings' table. For this Cochrane Review, we selected key outcomes for inclusion in 'Summary of findings' tables. We produced tables for all comparisons for which any numerical data were available. Within each 'Summary of findings' table, we listed the specified outcomes whether or not the included studies measured or reported them.

We intended to perform subgroup analyses for sex, age, severity of CTS symptoms, and studies at high versus studies at low risk of bias. However, sufficient information was not available for these subgroup analyses.